Tumour necrosis factor alpha gene polymorphisms and hospital outcomes in acute pancreatitis

A dissertation submitted in partial fulfillment of the requirements for
DM (Gastroenterology) examination of the
Tamil Nadu Dr. M.G.R. Medical University, Chennai,
to be held in August 2014

Certificate

This is to certify that the dissertation entitled "**Tumour necrosis factor alpha gene polymorphisms and hospital outcomes in acute pancreatitis**" is a bona fide work done by **Dr Jiffy Rasak V.A, Christian Medical College, Vellore** under my guidance and supervision in partial fulfilment of the university rules and regulations for **D.M Gastroenterology** examination of the Tamil Nadu Dr M.G.R Medical University to be held in August 2014

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Sub: **Fluid Research grant project NEW PROPOSAL:**
Tumour necrosis factor alpha gene polymorphisms and hospital outcomes in patients with acute pancreatitis
Dr. Jiffy Rasak V., Senior Registrar, GI Sciences, Dr. Ebby George Simon, Dr. B.S Ramakrishna, Dr. Pugazhendhi .S, GI Sciences, CMC

Ref: IRB Min. No. 7811 dated 18.04.2012

Dear Dr. Rasak,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Tumour necrosis factor alpha gene polymorphisms and hospital outcomes in patients with acute pancreatitis" on April 18, 2012. I am quoting below the minutes of the meeting

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Informed Consent Form and Patient Information Sheet (English, Tamil, Hindi, Telugu and Bengali)
3. A CD containing documents 1 – 2

The following Institutional Review Board (Ethics Committee) members were present at the meeting held on April 18, 2012 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore- 632002.

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We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent and requires a copy of the final report.

A sum of Rs. 80,000 /- (Rupees Eighty Thousand only) will be sanctioned for 18 months.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

c/c: Dr Ethy Guy Sisson

Acknowledgement

I take this opportunity to express my sincere gratitude to my guide, Dr Ebby George Simon, Professor, Department of Medical Gastroenterology, for his guidance, encouragement and constant support in undertaking and completing this project.

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CONTENTS

Introduction

Acute pancreatitis is a condition characterized by acute inflammation of the pancreas. In many instances the inflammation involves the peripancreatic soft tissue also. In majority of cases the inflammation is precipitated by pancreatic injury caused by either alcohol or gall stones[1]. However many other precipitating factors have been described to cause acute pancreatitis. In about 10% of cases of acute pancreatitis no aetiology can be found[1]. The key initial event in the pathophysiology of pancreatitis is premature activation of pancreatic enzymes[2]. The mechanism that triggers this initial enzyme activation is still unknown. Once activated, trypsin leads to the enzymatic activation of other pancreatic enzymes like phospholipase A2, kallikrein and elastase. This premature activation can lead to autodigestion of the pancreatic tissue. The activated lipase can lead to peripancreatic fat necrosis. The circulating enzymes can also lead to systemic effects like increased capillary permeability, vasodilation and disseminated intravascular coagulation. Phospholipase A2 is known to have potent cytolytic effects. This enzyme can degrade pulmonary surfactant and is thought to be one of the major mechanisms of pulmonary injury in acute pancreatitis[3]. The activated trypsin activates complements and kinins. These factors probably play a part in disseminated intravascular coagulation, renal failure and shock[4].

A variety of cytokines are activated by pancreatic inflammation. These cytokines play a major role in mediating the systemic inflammatory response syndrome and organ failure in acute pancreatitis[5]. TNF alpha is one of the major cytokines that is released in response to early pancreatic injury.

However in about 80% of the patients with acute pancreatitis the disease remains mild without any major local or systemic complications. The remaining 20% of the patients develop severe pancreatitis with local and systemic complications [6]. In mild acute pancreatitis

the mortality is less than 1%. However in severe acute pancreatitis, mortality can reach upto 25%[7]. Fifty percent of the deaths due to severe acute pancreatitis occur within the first two weeks of illness [8]. Systemic inflammatory response syndrome and organ failure accounts for majority of these deaths. Infective complications mainly infected pancreatic necrosis and sepsis accounts for most of the cases with late mortality. Even though there are various prognostic scores which can predict severe pancreatitis, it is still unknown why some patients develop mild pancreatitis and others develop severe disease. TNF alpha polymorphisms have been shown to affect the severity of pancreatitis through a modifier effect i.e. ,they do not per se cause pancreatitis but once pancreatitis sets in, those with these polymorphisms develop a more severe disease compared to those without[9]. The G→A transition at position 308 in the promoter region of TNF alpha gene is one of the most commonly studied polymorphisms[9]. However the results of such studies have been conflicting.

AIMS AND OBJECTIVES

1. To study the clinical profile and in- hospital outcomes of patients presenting with acute pancreatitis
2. To determine whether there is any association between TNF alpha gene polymorphisms [TNF 308 G/A(rs1800629), TNF 857 C/T (rs1799724) ,TNF 863 C/A (rs1800630)]with the severity of illness and hospital outcomes in patients with acute pancreatitis.

Review of Literature

Acute pancreatitis- mortality and incidence

One of the earliest descriptions of acute pancreatitis was given by Reginald Fitz (1889) defines it as a condition characterized by pancreatic haemorrhage, gangrene and disseminated fat necrosis[11]. Most episodes of this disease are mild and self-limiting. About 20% of the patients develop severe attacks with both local and systemic complications[12]. The overall mortality of acute pancreatitis is about 5-10% which can go up to 35% or higher if complications develop[13]. In spite of the advances in medicine and critical care, the mortality due to pancreatitis has not come down significantly[14].The incidence of acute pancreatitis is known to differ in different geographical regions due to the differences in alcohol consumption or in incidence of gallstones disease[15,16]. The incidence of acute pancreatitis has increased during the past few years in many countries[17] .This rise is probably secondary to increasing alcohol consumption and a rising prevalence of obesity and gallstone disease.

Pathophysiology

The exocrine pancreas secretes about 1500 - 2000 ml of fluid and 150 - 200 mmol of HCO_3^- daily in response to secretin, and secretes amylolytic, lipolytic and proteolytic digestive enzymes in response to cholecystokinin or muscarinic cholinergic stimulation[18].Enzymes for proteolysis are secreted in an inactive precursor form. These have to be activated to their active forms by trypsin. Trypsinogen, the precursor of trypsin is converted to its active form with the help of enterokinase,an enzyme secreted from the mucosa of duodenum.Otherproteolytic enzymes like chymotrypsinogen, proelastase, procarboxypeptidases and lipolytic and amylolytic enzymes are converted to their active form with the help of trypsin. These enzyme precursors are stored in the zymogen granules. There are various antitrypsins(inhibitors of trypsin) like pancreatic secretory trypsin inhibitor,α_1-

antitrypsin and α_2-macroglobulin. The above mentioned mechanisms protect the pancreas from enzymatic digestion. When these mechanisms fail, there will be premature activation of pancreatic proenzymes thereby leading to pancreatic parenchymal damage.

The initial abnormality causing the activation of precursor enzymes has been postulated to be a persistent increase in cytosolic calcium within the pancreatic acinar cell which leads to intracellular activation of the digestive enzymes[19].

Various mechanisms have been proposed to explain why the natural defences against unbridled pancreatic enzyme activation fail.

1. **Pancreatic duct hypertension-**An increase in the pancreatic ductal pressure resulting from outflow obstruction by any cause like a stone, oedema or sphincter spasm might rupture the small pancreatic ducts and cause extravasation of pancreatic juice into the gland[20].
2. **Duodenopancreatic reflux-** Reflux of duodenal contents through the papilla leads to the activation of trypsinogen to trypsin by the intestinal enterokinase[21]. The reflux can occur through a papilla that has been made incompetent by inflammation caused by various mechanisms (eg: alcohol, passed out stone, endoscopic cannulation or surgery). The activated trypsin leads to activation of phospholipase A2. Phospholopase A2 acts on lecithin (which is a normal constituent of the bile) and forms lysolecithin. Lysolecithin damages pancreatic cell membranes leading to progressive tissue damage and edema of the pancreatic ducts [22].
3. **Reduced apical exocytosis of pancreatic zymogens-** It has been proposed that in acute pancreatitis, there is increased intracellular accumulation of zymogen granules, consequent to a decreased in apical secretion and a normal rate of production. With increased accumulation, some of these granules eventually fuse with lysosomal membranes. Within the lysosomes, the enzyme cathepsin B activates trypsinogen to trypsin. The activated trypsin activates other zymogens causing progressive tissue damage [23].
4. **Hypersecretion-** In rare situations like organophosphorous poisoning, the disease may be caused by an excess secretion of enzymes due to excess muscarinic stimulation [24].

The non-infectious destruction of the pancreatic tissue by the above mechanisms leads to an inflammatory reaction at the site of injury (which is the normal response of human body to any injury). However what makes pancreatitis different is its propensity to amplify this localized process into a systemic inflammatory response syndrome (SIRS)[25]which inturn is responsible for its morbidity and mortality[26]. Acinar injury leads to expression of endothelial adhesion molecules(e.g., VCAM-1) which leads to recruitment of leucocytes and propagation of the inflammatory response[27]. In early stages of pancreatitis, it has been found that the activation of complement system and the subsequent release of C5a play significant roles in the recruitment of macrophages and polymorphonuclear leukocytes[28].Active granulocytes and macrophages release proinflammatory cytokines. The major proinflammatory cytokines include TNF alpha, IL-1, IL-6, IL-8, and platelet-activating factor (PAF).Proinflammatory cytokine release is usually followed by the release of anti-inflammatory cytokines (IL-2, IL-10, IL-11) that attempts to down-regulate inflammation[29].

SIRS is common in patients with acute pancreatitis and is probably mediated by activated pancreatic enzymes (phospholipase, elastase, trypsin) and cytokines (TNF, PAF) which are released into the portal circulation from the inflamed pancreas[30].Thesecytokines reach the liver and activate the hepatic Kupffer cells, which in turn induces hepatic expression and secretion of cytokines into the systemic circulation. This cytokine storm amplifies SIRS and in some cases leads to multiorgan dysfunction and death[31]. The circulating pancreatic enzymes can also lead to systemic effects like increased capillary permeability, vasodilatation and disseminated intravascular coagulation. The vasodilatation and increased capillary permeability secondary to the inflammatory mediators lead to many of the systemic complications like hypotension, third space fluid loss and acute renal failure. Myocardial depression secondary to vasoactive peptides might also contribute to hypotension. The

activated trypsin also activates complements and kinins. These factors are postulated to play a part in disseminated intravascular coagulation, renal failure and shock [4]. ARDS could be induced by active phospholipase A2 (lecithinase) which digests lecithin,a major component of lung surfactant.

Local complications- The initial tissue injury and inflammation leads to increased expression of endothelial adhesion molecules. This leads to enhanced recruitment of leucocytes and macrophages to the site of injury. These cells in turn produce further proinflammatory cytokines and enhance inflammation. Increased vascular permeability secondary to inflammation leads to edema of the gland- interstitial/edematous pancreatitis. Experimental models have shown that microcirculatory changes including vasoconstriction, capillary stasis, decreased oxygen saturation and progressive ischemia occur in acute pancreatitis. Mediators of inflammation like arachidonic acid metabolites (prostaglandins, PAF, leucotrienes), nitric oxide and reactive oxygen species interact with pancreatic microcirculation to increase vascular permeability, induce thrombosis and haemorrhage thereby causing pancreatic necrosis. In some patients, ischemia and severe inflammation of the gland can lead to disruption of the main and secondary pancreatic ducts leading to local fluid accumulations within and surrounding the pancreas that can later develop into pseudocysts[32].Pancreatic fistulas are also caused by disruption of the pancreatic duct and should be suspected in patients who develop massive ascites or pleural effusions[33].Infection of the necrotic pancreatic tissue or pseudocyst leading to an infected pancreatic necrosis or an infected pseudocyst can occur from the blood stream or from translocation of bacteria from the gut into the lymphatics. Under normal circumstances, translocation of gut bacteria does not occur because of the complex immunologic and morphologic barriers present. However, during acute pancreatitis, these barriers are down resulting in local and systemic

infection[34].The likely explanations for the penetration of the gut barrier by enteric bacteria are gut ischemia secondary to hypovolemia and pancreatitis-induced arteriovenous shunting in the gut[35].

Cytokines

Cytokines are a group of low molecular weight proteins (usually 16 to 25 kDa) that are produced within numerous cell types as a means of cell to cell communication[36]. Each cytokine has the ability to act on many different target cells rather than a single cell type. This property is termed pleiotropism. Cytokines also exhibit redundancy. This means that different cytokines can induce an identical biologic effect. Once a cytokine is produced, it has the ability to stimulate enhanced production of itself as well as many other cytokines, resulting in amplification of the inflammatory process and the development ofcascades[25]. Cytokines are usually active in very small (femtomolar) concentrations and their productionis tightly regulated[37.] Barring a few exceptions, cytokines are not constitutively produced. Instead, the cell of origin is activated to produce new cytokine mRNA during times of stress or in response to an external stimulus. In most instances, the tissue levels of cytokines are more important for the biological effects than the blood levels [25].

Cytokines in acute pancreatitis

Many authors have reported that the circulating levels of various cytokines (IL-6, IL-8, TNF alpha) are higher in patients with complicated and severe pancreatitis when compared to mild cases [37,38]. IL-1 and TNF are the primary members of the inflammatory cytokine family. They are primary inducers of IL-6 and IL-8 production. All of the serious consequences of severe sepsis such as fever, circulatory collapse, cardiac dysfunction , metabolic acidosis, and the production of ARDS are known to be initiated by TNF alpha and IL-1[40]. Almost all

experimental models of pancreatitis have implicated IL-1and TNF as the major pathologic cytokines associated with local and systemic tissue complications [25]. Studies on circulating human monocytes and polymorphonuclear leucocytes have shown that TNF, IL-6 and 1L-8 production was higher in patients with acute pancreatitis. Another important observation was that leucocytes from patients with complicated pancreatitis were hyperstimulated when compared to those from patients with mild pancreatitis [41,42].

During early hours of acute pancreatitis, pancreatic parenchyma produces 1L-1, TNF and IL-6 [43]. However the predominant source of cytokines in acute pancreatitis is the invading leucocytes. An important observation made from experimental models of acute pancreatitis was that the concentration of TNF and IL-1 within pancreatic tissues was substantially higher than the serum levels, levels that are known to be toxic to many cell types[44]. Grewal et al have shown that levels of TNF alpha in the portal vein of animals with pancreatitis was significantly higher than corresponding systemiclevels[45]. They postulated that the liver was serving to clear TNF thereby preventing it from reaching the general circulation. The expression of TNF receptors was also found to be increased during acute pancreatitis.de Beaux and colleagues have shown that the serum levels of TNF receptors predicted organ failure during AP even when TNF itself was not detectable[46]. IL-1 and TNF are both produced systemically during pancreatitis in addition to local production[47]. Some studies have shown that the production of IL-1 and TNF in the pulmonary parenchyma could be directly linked to ARDS in sepsis and acute pancreatitis [48]. Almost all animal studies have conclusively proved that these cytokines alone cannot initiate pancreatitis. Perfusion of the isolated human pancreas with high doses of IL-1 and TNF have shown little evidence that these agents can initiate an attack of acute pancreatitis[49]. However studies on gene knockout animals have proven beyond doubt that these agents play a role in determining the severity of

acute pancreatitis. When acute pancreatitis is induced in animals devoid of IL-1 or TNF receptors, they fail to develop maximal pancreatitis[50].Pancreatitis does develop in these transgenic animals, yet its severity/lethality never reaches that of wild-type mice. These studies thereby establish that although pancreatitis is not initiated or triggered by 1L-1 or TNF, they both play an important role in its progression.

Several investigators have demonstrated that acute pancreatitis is associated with the induction of acinar cell apoptosis, the degree of which might determine the severity of pancreatitis[51].When pancreatic acinar cells in vitro are exposed to high concentrations of TNF as found in pancreatic tissues during pancreatitis, a large portion becomes apoptotic[51].

Various animal studies have shown that TNF blockade during acute pancreatitis would decrease pancreatic necrosis and inflammation and decrease mortality by about fifty percent[52,53].

TNF alpha gene polymorphisms -The gene that encodes for TNFα is located on the short arm of chromosome 6 within the major histocompatibility complex (MHC) class III[54].Tumor necrosis factor production is regulated at the transcriptionallevel[55].Evidence from experimental and clinical studies has suggested that increased secretion of tumour necrosis factor-α (TNF-α) and interleukin-1β (IL1-β) is important in mediating organ dysfunction in severe acute pancreatitis[25,46].Genetic factors might influence levels of cytokine production[56]. Certain polymorphisms in the TNF alpha gene has been found to be associated with increased levels of TNF alpha production [57-59]. Such genetically determined differences in levels of cytokines following an insult might explain individual differences in disease severity in a variety of inflammatory disorders such as acute pancreatitis. If disease severity can be shown to be positively predicted by these polymorphisms, they might serve as excellent prognostic markers for these diseases since the direct measurement of these cytokines in blood is often

erratic in view of the intermittent nature of secretion, low half life of cytokines in circulation and clearance by the liver[42]. Moreover in diseases like pancreatitis it might be the tissue levels of these cytokines that are more important than the blood levels.

TNF alpha polymorphisms in diseases

In a study from Taiwan, Lu et al. studied 424 dyspeptic patients with H.pylori infection. They studied TNF-alpha promoter SNP over the locus on -1031(T/C), -863(C/A), -857(C/T), -806(C/T), and -308(G/A) by sequence-specific oligonucleotide probe[60]. They found that among the H. pylori-infected patients, those with -1031C or -863A allelles of TNF-alpha promoter had more severe gastric neutrophil infiltration and TNF-alpha gastric staining than individuals with -1031TT or -863CC genotype. They also found that -1031C and -863A carrier status were independent risk factors for developing duodenal and gastric ulcers in H. pylori-infected hosts.

In study from Australia, O'Callaghanet al studied more than 600 patients with IBD[61].They studied the *TNF* alpha promoter polymorphisms at positions -1031T/C, -863C/A, -857C/T, -308G/A by PCR-RFLP method. They found that the TNF alpha -857C allele was strongly associated with the risk of IBD. Previous studies had already shown that the TNF alpha -857C allele was associated with increased expression of TNF alpha in IBD [62].

Studies have also shown that TNF alpha promoter region polymorphisms are associated with poor outcomes in patients with cerebral malaria and meningococcal disease [63,64].

In a study of 106 critically ill patients, Surbatovicet al. have studied their outcomes and the relation to TNF-α308, IL-101082, CD14159, and IL-1ra gene intron2 genotype

polymorphisms [65]. Nearly half of these patients had severe sepsis secondary to trauma. There were fifteen patients with acute pancreatitis. Distribution of 3 TNF-α308 genotypes (AA, AG, GG) was associated with primary outcome (death) with statistical significance. All the patients with AA genotype survived (7/7). Relative risk of death with AG genotype was 3.250 and with GG genotype was 1.923. No significant association of the TNF genotype was found with the type of microorganism or the underlying cause of sepsis.

In a study from Taiwan, Chang et al. have studied TNF alpha polymorphisms in patients with chronic pancreatitis[66]. They studied 70 cases (48 men and 22 women) and 286 control subjects (151 men and 135 women). They studied five TNF alpha promoter polymorphisms (-1031, -863, -857, -308, and -238) using direct sequencing.The-863A allele of the TNF-alpha promoter was found to be associated with an increased risk for chronic pancreatitis (odds ratio (OR) 4.949 (95%confidence interval (CI) 2.678–9.035).

Chang et al have studied a group of 126 hypertriglyceridemia patients in Taiwan [67]. 46 of these patients had history of pancreatitis (probably secondary to hypertriglyceridemia) and 80 patients never had a pancreatitis episode. The authors tried to study why some people with hypertriglyceridemia developed pancreatitis while others did not. They studied *TNF* promoter polymorphisms (nucleotide positions 1031, 863, 857, 308, and 308) by direct sequencing. They also studied mutations in PRSS1, SPINK1 and CFTR genes. They found that *TNF* promoter 863A allele was an independent risk marker for pancreatitis in patients with hypertriglyceridemia.

TNF alpha polymorphisms in acute pancreatitis

One of the earlier studies on the association of TNF alpha gene polymorphisms and the severity of acute pancreatitis was published in 2001[68]. In this study, Powell et al studied 190 patients with acute pancreatitis and 102 healthy volunteers. Of the 190 patients, 113 patients had mild disease and 77 patients had severe disease. Alcohol was the commonest aetiology in both the groups. They had used the 1992 Atlanta classification system to classify mild and severe disease. Mortality was 2% in the mild group and 22% in the severe group.

TNF (TNF-308, TNFB), IL-1β, and IL-1 receptor antagonist (IL-1ra) genotypes were determined for both the patients and the control group. The TNF-308 polymorphism occurred with equal frequency in both cases and controls. Moreover there was no difference in the distribution of the mutant allele between the patients with mild and severe pancreatitis.
Furthermore *TNFB*, IL-1β, and IL-1 receptor antagonist (IL-1ra) genotype polymorphisms also did not show any significant difference between mild and severe pancreatitis and also between cases and controls.

In 2003 another study on TNF alpha gene polymorphisms and acute pancreatitis was published by Zhang et al. from China[69]. In this study they included only patients with biliary pancreatitis. A total of 127 patients and 102 healthy controls were studied. The diagnosis of acute pancreatitis was based on clinical criteria, an increased amylase and lipase activity (enzymatic colorimetric test) in serum and CT evidence of pancreatitis. Severe pancreatitis was diagnosed in those patients with an APACHE score of ≥ 8 or CT severity index of ≥ 4. They had used the ACCP/SCCM consensus criteria for the diagnosis of septic shock. The controls were healthy volunteers. They studied the TNF alpha -308 polymorphism in the

promoter region of TNF alpha gene and another polymorphism at position +252 in the first intron of TNF β. They also measured plasma TNF alpha levels in all patients with acute severe pancreatitis at admission. Of the 127 patients 61 patients had severe pancreatitis and the rest had mild disease. 18 patients had documented septic shock .The TNF-308 polymorphism, TNF2 was found in18 (29.5 %) of patients with severe pancreatitis compared with 17 (25.8 %) of patients with mild pancreatitis. There was no significant difference. Further there was no significant difference in the distribution between cases and controls. A similar insignificant result was found for TNF β polymorphism also. Among the 61 patients with severe pancreatitis, TNF alpha levels at admission were similar in those patients who developed septic shock and those who did not. There was no significant correlation between the TNF alpha- 308 polymorphisms and plasma TNF alpha levels at admission in the patients studied. This study however found a significant difference in the TNF alpha- 308 polymorphism distribution when comparing patients with and without septic shock. TNF2 was found in 50 %of patients who developed septic shock compared with 20.1 % of patients with no septic shock (odds ratio- 5.155, *P*=0.023).

In 2005 Balog et al. had published a study from Hungary [9]. They had studied TNF-alpha, HSP70-2, and CD14polymorphisms in patients with acute pancreatitis and tried to correlate the polymorphisms with disease severity. It was a prospective single centre trial from a teaching hospital in Hungary. Acute pancreatitis was diagnosed based on the clinical history consistent with pancreatitis, radiologic evidence, and a serum amylase level greater than 660 U/L. They recruited a total of 77 patients with acute pancreatitis. 71 healthy controls were also included. Alcohol was the commonest aetiology in this series and in eight out of 77 patients, no cause could be identified. They classified the disease as mild or severe based on the original Ranson's criteria. Those patients with a score of less than three were classified as

mild and those with a score of ≥3 were classified as having severe pancreatitis. The diagnosis of infected pancreatic necrosis was made based on the cultures of pancreatic tissue obtained by either USG or CT guided procedures. Twenty nine of the 77 patients had mild disease and forty eight patients had severe disease based on their definition. Of the patients with severe pancreatitis 20 patients had infected pancreatic necrosis. In both cases and controls they studied the TNF alpha -308 polymorphism by PCR-RFLP method. There was no statistically significant difference in the distribution of the TNF alpha -308genotype between the patients and the healthy controls. However the GA genotype was more common in patients with severe pancreatitis compared to those with mild disease with an odds ratio of 3.145. The number of homozygotes for the inflammatory allele (AA genotype) was very low in this study (2 out of 77 patients)

Tukiainen et al have studied TNF alpha, CD-14, HSPA1B genes in patients with acute pancreatitis.[70]. They studied 397 patients with acute pancreatitis and 300 healthy controls. Of the 397 patients, 214 had alcohol induced pancreatitis. It was a single centre study from Helsinki university hospital. The diagnosis of acute pancreatitis was based on the typical clinical signs of abdominal pain accompanied by plasma amylase level more than 3 times the normal upper limit, or a positive CT scan finding. They had excluded all patients with chronic pancreatitis and all patients with more than three episodes of acute pancreatitis in the past. The disease was classified as mild or severe based on the 1992 Atlanta criteria. Patients with organ failure requiring either mechanical ventilation or dialysis were classified as a separate subgroup of severe pancreatitis. Septic complications were defined as positive blood cultures or positive cultures from abdominal drains or operative samples. Of the 397 patients studied, 152 had severe pancreatitis. Of these 152 patients with severe pancreatitis, 55 patients had severe pancreatitis with organ failure. Five patients had succumbed to the disease

during hospital stay. 74 patients had past history of acute pancreatitis. They studied the TNF promoter-308 G/A (rs1800629) polymorphism in this study. The distribution of the genotypes was in Hardy-Weinberg equilibrium for the TNF polymorphism. There was no significant difference in the TNF alpha genotype distribution between the mild and severe pancreatitis cases. The genotype distributions of the subgroup of patients with organ failure and the patients with mild acute pancreatitis were also comparable. There were 47 patients with septic complications. The distribution of TNF alpha polymorphisms were similar between this group and patients with mild acute pancreatitis without any infective complications. There was no significant difference in the TNF alpha genotype distribution between cases and healthy controls. Till 2008, this was the study on TNF alpha polymorphisms in acute pancreatitis with the largest sample size.

In another study published in the same year (2008) de-Madaria et al. reported their experience with TNF-238 polymorphisms[71]. It was a single centre prospective study from Spain. Consecutive patients with acute pancreatitis were included. Exclusion criteria were age under 18 years, admission after 48 hours of the onset of the symptoms, any chronic inflammatory disease, concurrent infections, neoplastic diseases, chronic renal failure and chronic liver disease. In this study, all patients received prophylactic antibiotics (imipenem 500 mg every eight hours).All the patients with SIRS, APACHE score ≥ 8, or CRP level >15 mg/dl or any organ failure underwent a contrast enhanced CT abdomen at 72 hours after admission. The disease was classified as mild or severe based on the Atlanta 1992 criteria. All the local and systemic complications were also defined as per the Atlanta 1992 criteria. Mortality was defined as death during admission and any death after discharge secondary to a complication of pancreatitis. A blood sample was obtained within 72 hours after the onset of symptoms from all patients for cytokine levels and genetic polymorphisms. They had studied

the TNF alpha-308 and TNF alpha-238 polymorphisms by PCR RFLP method. A total of 84 patients were studied. Sixty six percent of the patients had biliary pancreatitis. Twenty one patients (25%) had severe pancreatitis. Nine patients had organ failure and fifteen patients had local complications. Of the eighty four patients studied, two patients died due to multiorgan failure.

The GA genotype of the TNFalpha -238 polymorphism was associated with more frequent organic failure than the GG genotype. The TNF alpha -308 polymorphism did not show any statistically significant correlation with the outcomes of acute pancreatitis. The observed frequency of single nucleotide polymorphisms were in accordance with the Hardy-Weinberg equilibrium. Both the polymorphisms studied did not show any correlation with the cytokine levels in the patients studied.

In 2010, Ozhan et al. published another study on the outcomes of pancreatitis and TNF gene polymorphisms. The study was from a teaching hospital in Turkey[72]. Two polymorphisms in the promoter region (positions −308 and −238) in TNFα gene were studied. They recruited 103 patients with acute pancreatitis and 92 healthy controls .The criteria for diagnosis of AP were: a clinical history consistent with the pancreatitis, radiological evidence, and serum amylase level greater than 3 times the upper limit of normal. The patients were recruited at the time of admission. The progress of the patients during the hospital stay was followed up. The disease was classified as mild or severe based on Atlanta 1992 criteria. There were 68 patients with mild pancreatitis and 35 patients with severe disease. The TNF alpha gene polymorphisms were studied by PCR-RFLP method. The observed frequency of all SNPs satisfied the Hardy-Weinberg equilibrium. Genotype distribution of two SNPs (rs1800629; rs361525)in cases and controls did not show any statistically significant difference. There

was no difference in the distribution of TNF alpha gene polymorphisms studied between patients with mild and severe disease.

In one of the latest studies in this field published in 2012;Bishehsari et al evaluated 211 patients with acute pancreatitis and 401 controls[73]. The main outcomes studied were persistent SIRS and MODS (multi organ dysfunction syndrome). Persistent SIRS was defined as SIRS lasting for more than 48 hours. MODS was defined as failure of ≥2 organ systems (cardiovascular, pulmonary, and/or renal) persisting more than 48 h. Subjects were analyzed for the SNPs at -1031 C/T (rs1799964), -863 A/C (rs1800630), -857 C/T (rs1799724), -308 A/G (rs1800629), and -238 A/G (rs361525) in the TNF alpha gene. Twenty-three of 211 AP patients (11%) developed MODS. The distribution of the TNF gene polymorphisms were similar in the patients and the control group. However progression to MODS was associated with the minor allele at -1031C (56.5% vs. 32.4% P = 0.022, OR: 2.7; 95%CI: 1.12-6.51) and -863A (43.5% vs. 21.8% P = 0.022, OR: 2.76; 95%CI: 1.12-6.74).

Every single study published till date has proven beyond doubt that TNF alpha promoter polymorphisms do not increase the susceptibility to acute pancreatitis. The distribution of polymorphisms in every study is similar in both cases and controls. However the data on the effect of these polymorphisms on the outcome of pancreatitis is variable. There are some studies which have shown that these polymorphisms have a modifier effect on the outcome of pancreatitis whereas other studies have shown that these polymorphisms have no effect on the outcome of acute pancreatitis[9,68-73]. The sample size in most of these studies was arbitrary. A sample size calculation based on the prevalence of the polymorphisms of interest in the population studied was not done in most of the studies.

METHODS

Study design

This was a cross sectional study performed in the Christian Medical College, Vellore.

Inclusion criteria

Patients who presented to CMC Vellore with acute pancreatitis or complications of acute pancreatitis and who gave an informed consent to be part of our study were included in the study.

Diagnosis of acute pancreatitis was based on the following criteria

1. Pain characteristic of pancreatitis

2. Elevated serum amylase and lipase levels (>3 times upper limit of normal)

3. Imaging suggestive of pancreatitis

If any two of the above criteria were present, a diagnosis of acute pancreatitis was made

Study duration

September 2012 to December 2013.

Exclusion criteria

Patients with evidence of underlying chronic pancreatitis (ductal dilatation, ductal or parenchymal calcification).

Patient (or legally accepted representative) not willing to be part of the study.

Study setting and Population

The study was conducted in the department of Gastrointestinal Sciences in CMC Hospital, Vellore from September 2012– December 2013.

Methods

Patients were recruited to the study from either the emergency medical services or wards by the primary investigator after getting an informed consent. A detailed history and clinical examination was done at the time of recruitment. The blood sample for genetic analysis was taken at the time of recruitment. The clinical course of the patient was followed up by the primary investigator. The investigations and treatment decisions for the patient was decided by the treating unit .No additional clinical laboratory investigations were performed for the study other than those essential for clinical care. Consecutive patients were enrolled, subject to consenting. The genetic testing was performed in a research laboratory attached to the department by a specialist. The clinical investigator was blinded to the genetic data, while the molecular biologist was blinded to the clinical data. Any patient with either local or systemic complication was classified as having severe pancreatitis. Those patients without a local or systemic complication were classified as having mild pancreatitis. Atlanta 2012 classification was used to define local and systemic complications [10].

Sample size

From unpublished data from our department (on-going community based studies), we found that the inflammatory TNF alpha (TNF 308 G/A) genotype is present in approximately eight percent of our population and the TNF 863 AA genotype is 7.6%.The hypothesis was that

this single nucleotide polymorphism (or other SNPs in the same gene) may have a 'modifier' effect on the course of acute pancreatitis. Therefore we expect that eight percent of patients with acute pancreatitis would also have this inflammatory genotype.

Sample size calculation was done using the following assumptions:

In hospitalized cases with acute pancreatitis, we expect the cases of acute severe pancreatitis (ASP) to constitute 33% and acute mild pancreatitis (AMP) to constitute 67%. In control population we know that the frequency of the two major SNPs each is 8% or 0.08 of the population. To detect a significant association between ASP and the SNP with an Odds Ratio of 4, with a type I error of 0.05 and power of 0.80, we will need to study a total of 168 patients with acute pancreatitis.

Ethics Committee review

The Human Ethics Committee of CMC Vellore reviewed and approved the proposal and consent forms.

Genetic analysis

9 ml of venous blood samples were collected in EDTA coated tubes after obtaining informed written consent. DNA was isolated using standard salting out procedure. Genomic DNA from mononuclear cells in blood was extracted by salting out and stored at −20°C . All the three polymorphisms (rs1800629, rs1799724,rs1800630) were studied by PCR-RFLP methods. The PCR reactions were of 20 µlvolume and each reaction mix contained 1x taq DNA polymerase master mix Red (Ampliqon), and 250nM of forward and reverse primers (Shrimper).

The thermal cycling protocol for rs1800629, rs2227956, rs1799724, and rs1800630comprised of initial denaturation at 95℃ for 5 min, cycle denaturation at 94℃ for 30 sec, annealing

temperature at 57℃ for rs1800629, 55℃ for rs1799724 and 56℃ for rs1800630 a extension at 72℃ for 30 sec, and the cycle was repeated for 34 more times, final extension at 72℃ for 5 min. The PCR products were checked for amplification by resolving on 2% agarose gel electrophoresis and checked with UV transilluminator (VilbertLourmat).

The amplified samples were digested with restriction enzymes- NcoI two units overnight incubation at 37℃ for rs1800629(-308G/A), Tai I four units overnight incubation at 65℃ for rs 1799724(-857C/T) and rs1800630(-863C/A).The digested PCR products were resolved on 2% agarose gel electrophoresis and the gel patterns were documented using a gel documentation system (VilbertLourmat, France).

The genotypes were assigned for the PCR-RFLP analysis as given in the table.

SNP	Forward primer	Reverse primer	Product size	Restriction enzyme	Restriction fragments
rs1800629 TNF 308G/A)	5-AGGCAATAGGTTTTGAGGGCCAT-3	5-TCCTCCCTGCTCCGA TTCCG-3	I07 bp	Nco I 2 units	G-87 &20 A-107
rs1799724 (TNF 857C/T)	5-GGCTCTGAGGAATGGGTTAC-3	5-CCTCTACATGGCCC TGTCTAC-3	128 bp	Tai I 4 units	C-110&18 T-128
Rs1800630 TNF 863C/A	5-GGCTCTGAGGAATGGGTTAC-3	5-CTACATGGCCCTG TCTTCGTTACG-3	125 bp	Tai I 4 units	C-125 A-104&21

Statistical methods:

The data of the present study were recorded manually and into the computer and after its proper validation, checked for error, coding & decoding were compiled and analyzed using the software SPSS 11.5 for Windows. Categorical data was compared using the Pearson Chi

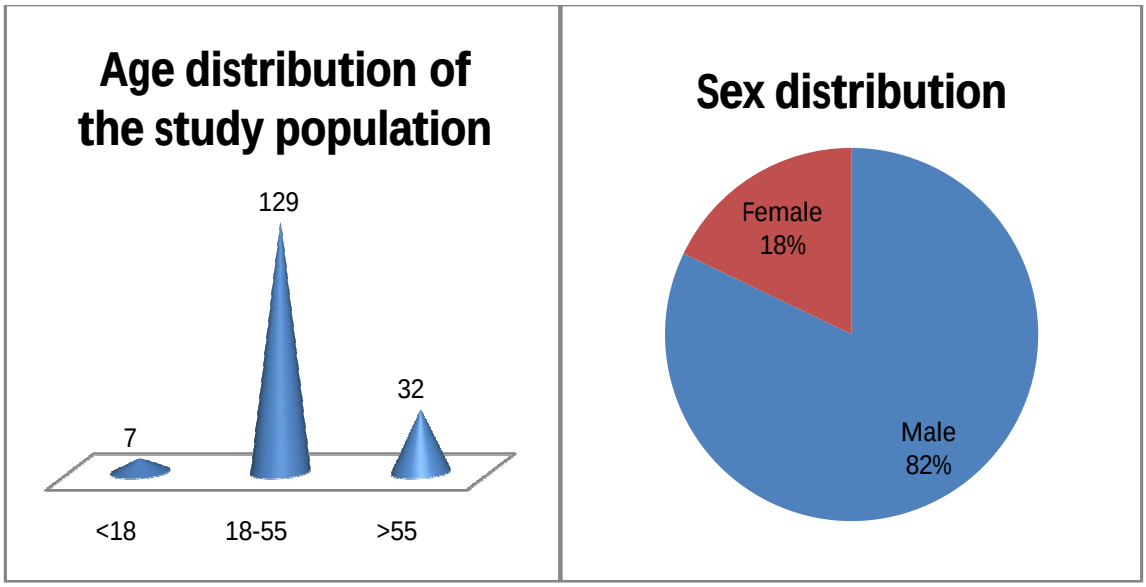
square test, while continuous data was compared using two-tailed independent t tests. All the continuous variables were expressed as mean ± standard deviation.

The Atlanta 2012 classification had included a new group called moderately severe pancreatitis for those patients with only local complications or systemic complications which last for less than 48 hours. For the purpose of analysis, the moderately severe group was also classified as severe pancreatitis. Those patients who were discharged against medical advice in a moribund condition were also classified as dead for the purpose of analysis.

RESULTS

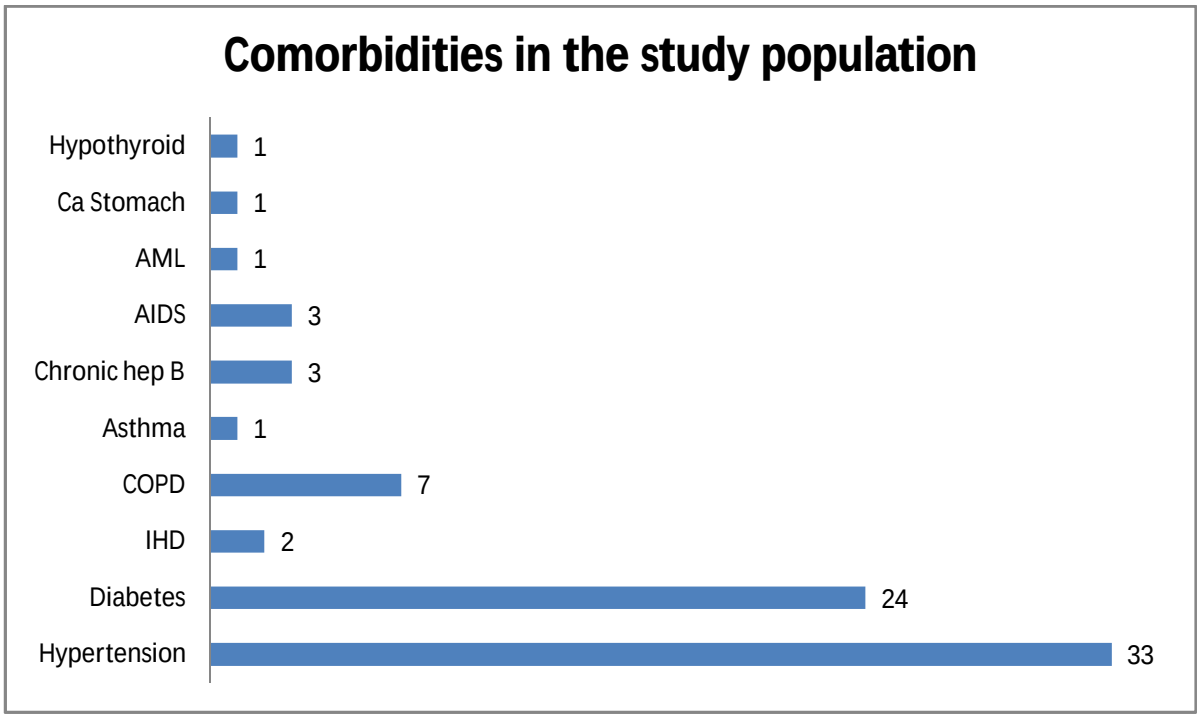
A total of 179 patients were recruited as part of this study between September 2012 and December 2013. Eleven of these patients were excluded due to underlying chronic pancreatitis on imaging. The remaining 168 patients who gave informed consent to be part of the study were included. Of these 168 patients, 164 were admitted to the wards and four patients were discharged from the emergency medical services. 151 patients presented directly to our centre with an acute episode of pancreatitis, whereas seventeen patients were initially managed elsewhere and thereafter presented to our centre with complications of acute pancreatitis.

Fig 1- Age and sex distribution of the study population



82% of the study population were males (138/168). Majority of the patients (76.7%) were in the age group of 18-55 years. 19% of the study population was >55 years and 4% of the patients were less than 18 years of age. The mean age of the study population was 40.55± 15.02 years. Sixty two (36.9%) patients had a comorbid medical illness. Hypertension was the commonest medical illness in the study population. Few patients had multiple comorbidities.

Figure 2- Comorbidities in the study population



Clinical Presentation

The patients with acute pancreatitis had presented to hospital after a median duration of three days after the onset of pain. All the patients had abdominal pain at the onset of symptoms. 98.8% of the patients had vomiting associated with pain. Thirty four patients (20.2%) had breathlessness at presentation. Three patients gave history of decreased urine output at presentation. Sixteen patients (9.5%) had documented fever at presentation. Twenty patients (11.9%) had hypotension at presentation. Table 1 shows the baseline parameters of the study population at presentation.

Table 1 - Baseline parameters of the study population at presentation

Particulars	**Total**
Total cases	168
Age(years)	40.55 ± 15.02
Male:Female	4.6 :1
SGS score	1.96 ± 1.55
CRP(mg/L)	110.37 ± 77.25
Amylase (U/L)	944.55 ± 938.79
Lipase(U/L)	1867.97± 2448.03
PCV (%)	41.52 ± 7.86

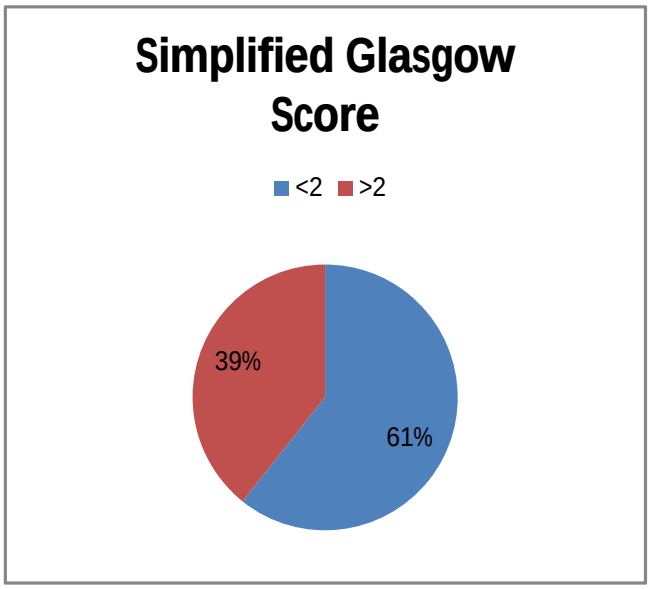
Abbreviations:

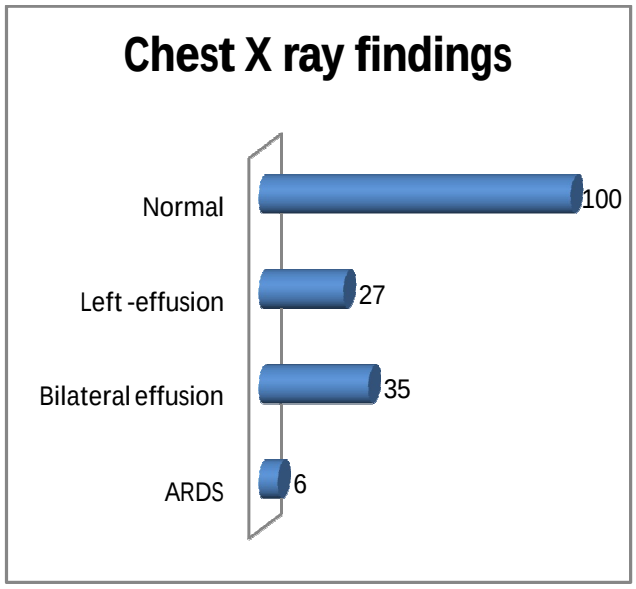
SGS – Simplified Glasgow score, CRP – C reactive protein, PCV – Packed cell volume

The mean age of the study population was 40.55±15.02 years. The Simplified Glasgow Score (SGS) at admission ranged from a minimum value of 0 to a maximum value of six, the median being two. SGS>2 was present in 66 patients at admission. The mean duration of hospital stay for the study population was 10.05±8.76 days. All patients underwent a chest X ray and ultrasound scan of the abdomen. A CT scan was done only in those patients where it was thought to be necessary by the treating physician. Eighty three patients out of the 168 underwent a CT scan at some point during the hospital stay.

Sixty eight patients (40.4%) had an abnormal chest x ray at presentation. Twenty seven (16.07%) patients had a left sided pleural effusion. Thirty five (20.8%) patients had bilateral effusion at presentation. An ARDS-like picture was present in six patients. Hundred patients had a normal chest X ray.

Figure 3- Simplified Glasgow Score and Chest X ray on presentation





The initial screening ultrasound scan showed a bulky/edematous pancreas in 149 (88.69%) of patients. An acute fluid collection was present at admission in 54 (32.14%) of patients.

Complications

During the course of hospital stay seventy two patients (42.85%) had one local complication of pancreatitis or other. Acute fluid collection was the commonest local complication which was present in 54 (32.1%) of the patients. Pancreatic necrosis and related complications like necrotic collection, walled off pancreatic necrosis were present in thirty three patients (19.6%).

An infected pancreatic necrosis was diagnosed based on the presence of air in the pancreatic parenchyma (indicating the presence of gas forming organisms) in a patient who had not undergone any interventional procedure or had a positive culture in a diagnostic aspirate from the pancreatic necrosis. A diagnostic aspirate was done only in those cases where the

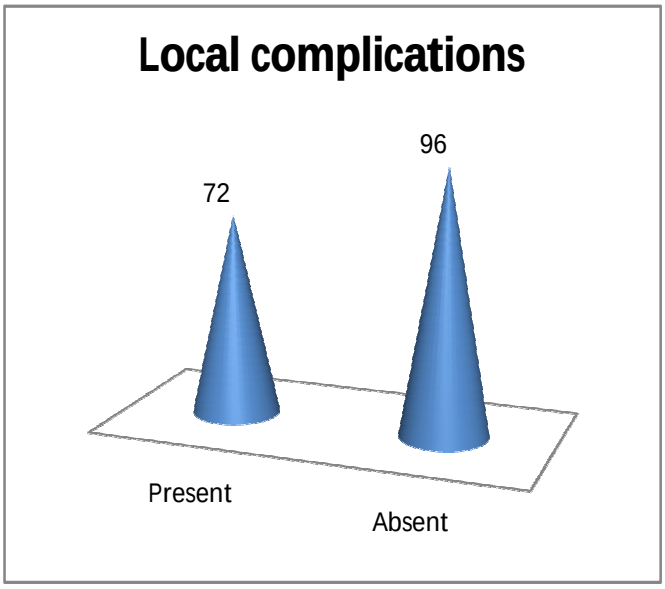
clinician suspected an infected necrosis. In our study population an infected pancreatic necrosis was proven based on imaging or culture in six patients.

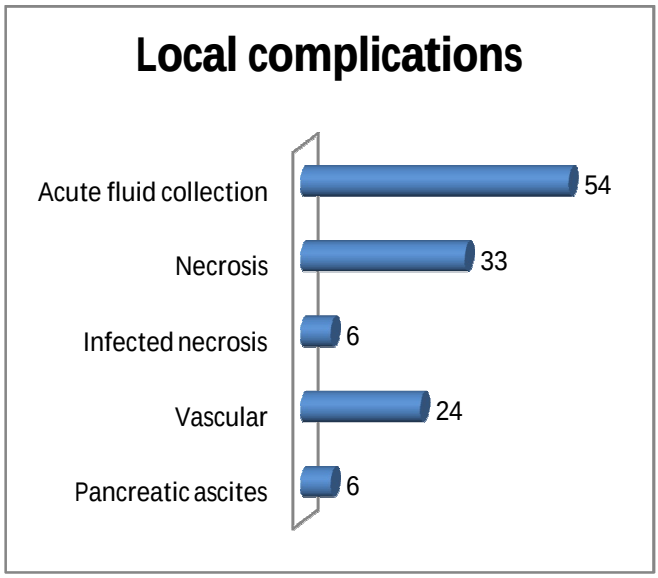
Twenty four (14.28%) patients had some vascular complication secondary to acute pancreatitis. Twenty three (13.69%) patients had splenic vein thrombosis. Nineteen(11.3%) patients had isolated splenic vein thrombosis. Two patients had splenic vein thrombosis and superior mesenteric venous thrombosis. Two patients had splenic vein thrombosis extending to the portal vein. One patient developed a jejunal artery pseudoaneurysm. This patient developed massive GI bleed during the hospital stay which settled following a coil embolization of the pseudoaneurysm.

As already discussed seventeen of our patients were treated elsewhere for acute pancreatitis and presented to our centre later on with some complication or the other. Of these seventeen patients, thirteen patients had presented with a pseudocyst of pancreas.

Pancreatic ascites is a local complication of severe acute pancreatitis caused by pancreatic duct disruption secondary to severe inflammation in acute pancreatitis. This condition is characterized by a high ascitic fluid amylase, lipase values and demonstration of duct disruption on imaging. Six of our patients developed pancreatic ascites during the course of hospital stay.

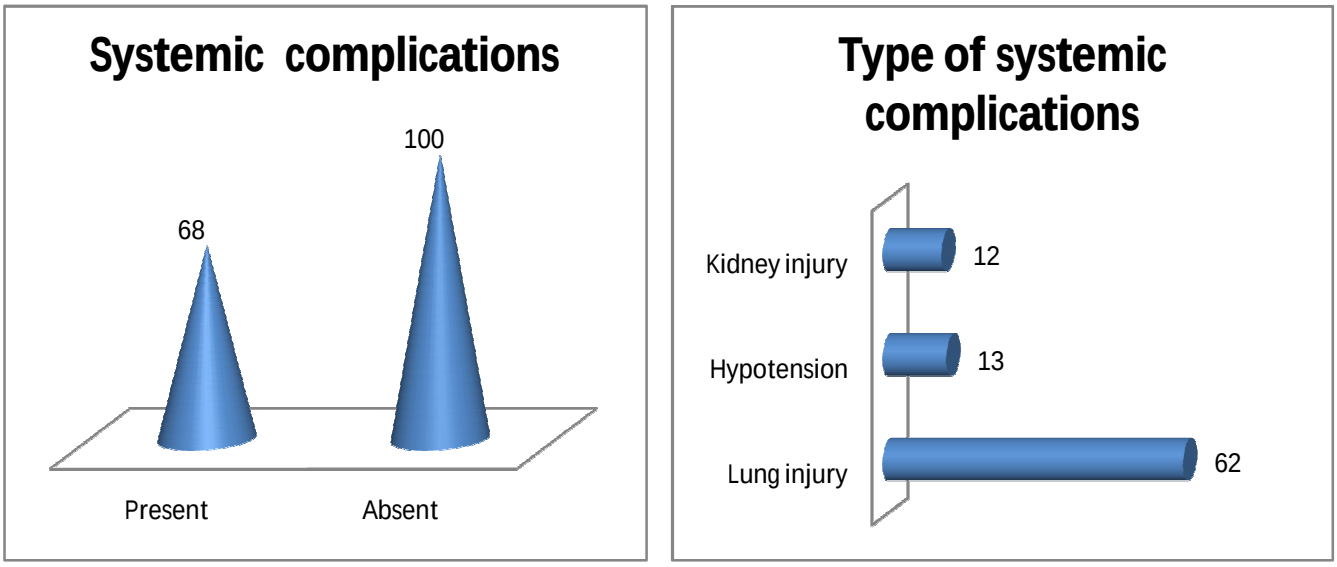
Figure 4- The spectrum of local complications in the study population





Sixty eight (40.47%) patients had a systemic complication of pancreatitis documented during hospital stay. In twenty three patients, the systemic complication was transient (lasting less than 48 hours), whereas in forty five patients the systemic complication was persistent (lasting more than 48 hours). Acute lung injury was the commonest systemic complication. Sixty two (36.9%) patients had acute lung injury as a complication of acute pancreatitis. Thirteen (7.73%) patients had documented hypotension as a complication of acute pancreatitis. Twelve (7.14%) had acute kidney injury as defined by a serum creatinine concentration of more than 1.9 mg/dl .

Figure 5 - Spectrum of systemic complications in the study population



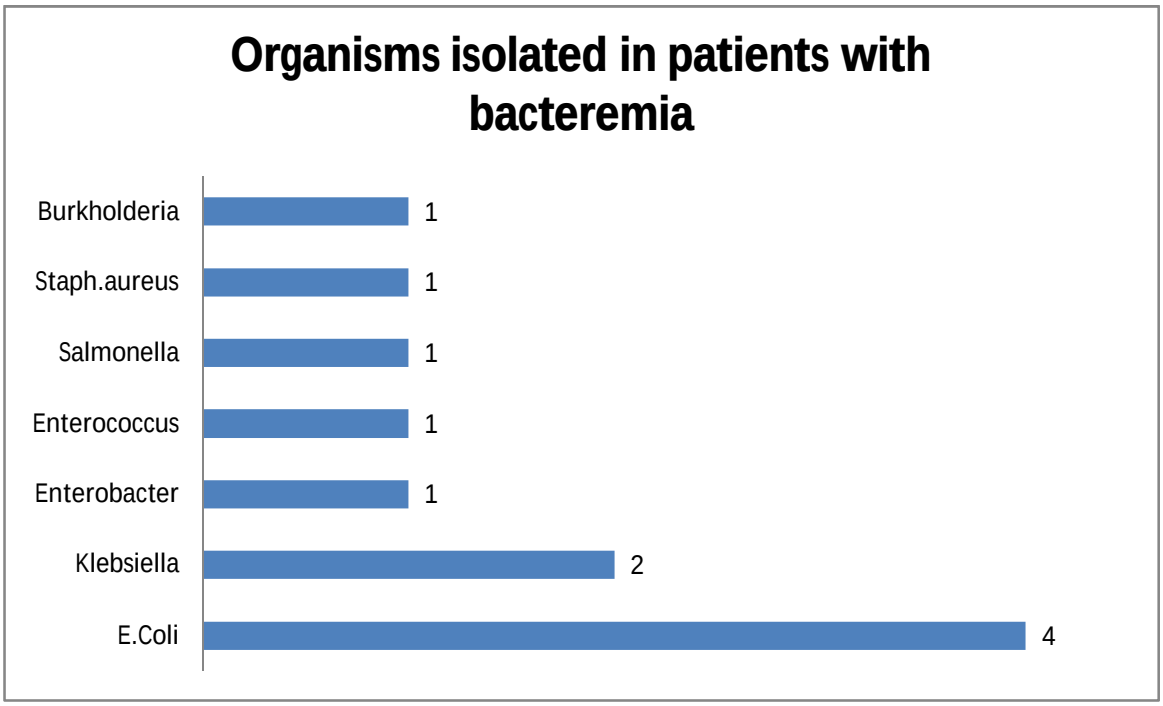
Infectious complications

During the course of hospital stay, eleven patients had proven bacteremia. E.coli was the commonest organism isolated. Six patients met the criteria for infected pancreatic necrosis (either a positive culture on diagnostic aspirate or imaging evidence). Figure 6 shows the spectrum of organisms identified on blood culture. Six patients had documented infected peripancreatic collections (diagnosed based on a positive culture from a diagnostic aspirate). Seven patients developed urinary tract infection during the hospital stay. Four patients developed hospital acquired pneumonia.

Table 2- The spectrum of infectious complications in the study population

INFECTIOUS COMPLICATION	**NO: OF PATIENTS**
Bacteremia	11
Infected pancreatic necrosis	6
Infected fluid collection	6
Urinary tract infection	7
Hospital acquired pneumonia	4

Fig 6- Organisms isolated in patients with bacteremia



Other complications

Three patients in the study population had exacerbation of underlying COPD during hospital stay. One patient had an unstable angina while he was admitted for acute pancreaitis. Two patients had pulmonary embolism while they were admitted for treatment of acute pancreatitis. During hospital stay for acute pancreatitis, four patients had GI bleed. Two of these patients had gastric ulcer and one patient had a duodenal ulcer. The fourth patient with GI bleed was diagnosed to have a jejunal artery pseudoaneurysm. This patient underwent a coil embolization of the jejunal artery and bleed was controlled. All the patients with ulcer disease improved with conservative management.

Etiology of acute pancreatitis

Alcohol and gall stone disease accounted for the etiology in 64.8% of our patients. There were seventy nine patients with alcohol induced acute pancreatitis and thirty patients with

gall stone induced pancreatitis. In forty two(25%) patients the cause of pancreatitis was not evident after extensive evaluation. They were labelled as idiopathic pancreatitis.

In five patients, hypercalcemia secondary to hyperparathyroidism was the etiology of acute pancreatitis. One of these patients with hyperparathyroidism came with a very severe attack of acute pancreatitis and died in the ICU. In all the other patients, parathyroid adenoma was diagnosed on further evaluation and they underwent surgery for the same. All these patients except one had come with the first episode of pancreatitis. None of them were known to have hyperparathyroidism prior to this attack of pancreatitis. Acute pancreatitis was the presenting symptom of hyperparathyroidism in these patients.

There were six cases of probable drug induced acute pancreatitis. There was one patient with recurrent acute pancreatitis in whom pancreas divisum was diagnosed on evaluation. There were four patients in the study population who presented with acute pancreatitis after an ERCP procedure. There was one patient in whom the evaluation of acute pancreatitis led to the detection of an ampullary neoplasm.

Table 3- Etiology of acute pancreatitis in the study population

ETIOLOGY	**NO: OF PATIENTS(n=168)**
Alcohol	78(46.4%)
Gall stones	30(17.8%)
Idiopathic	42(25%)
Hypercalcemia	5(2.9%)
Drug induced	6(3.5%)
Post ERCP	4(2.3%)
Pancreas divisum	1
Ampullary growth	1
Hypertriglyceridemia	1

Table 4- Drugs implicated as etiology in the study population

DRUG	NO: OF CASES
Anti retroviral therapy	2
L- Asparaginase	2
Prednisolone	1
Lamivudine	1

Patients with recurrent acute pancreatitis

There were twenty nine patients in our series who presented with recurrent acute pancreatitis. The number of past attacks in these patients ranged from two to eleven. The mean age of this population was 32±13.17 years. Twenty six (89.7%) of the twenty nine patients were male. Alcohol (48.27%) was the commonest etiology in this group. Eighteen patients had mild disease. Only two patients had persistent organ failure.

Table 5- Etiology of pancreatitis in patients with recurrent acute pancreatitis

ETIOLOGY	**NO: OF CASES(n=29)**
Alcohol	14(48.2%)
Idiopathic	11(37.9%)
Gall stones	2(6.8%)
Pancreas divisum	1(3.4%)
Hyperparathyroidism	1(3.4%)

Table 6- Baseline characteristics of patients with recurrent acute pancreatitis(n=29)

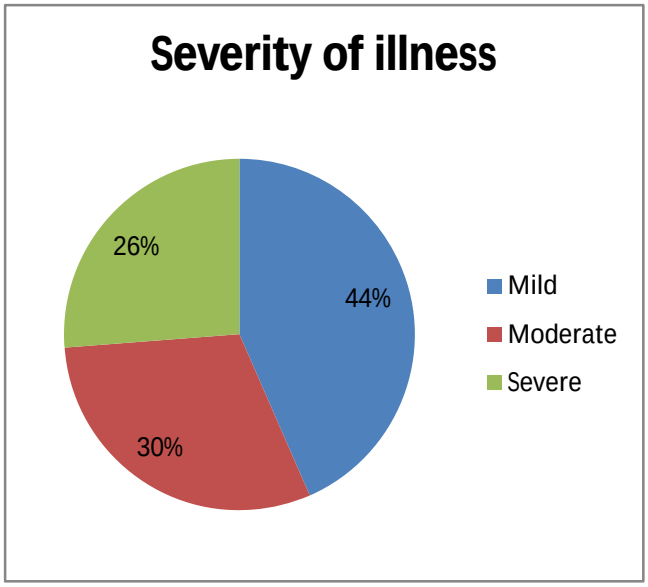
Particulars	**Value**
Age(years)	32.00± 13.17
Male:Female	8.6:1
SGS score(mean)	1±1.13
CRP(mg/L)	87.35±80.68
% of mild cases	62.06%

Abbreviations: SGS- Simplified Glasgow Scoring, CRP- C reactive protein

Severity of illness

Based on the presence of local and systemic complications, the patients were categorized into mild, moderate and severe as per the Atlanta 2012 criteria. There were seventy three(44%) patients with mild disease, fifty one patients with moderate disease (30%) and forty four (26%) patients with severe disease. By our study definition any patient with either a local or systemic complication was classified as severe pancreatitis. So as part of our analysis we clubbed together the patients with moderately severe disease and severe disease into a single group as severe pancreatitis.

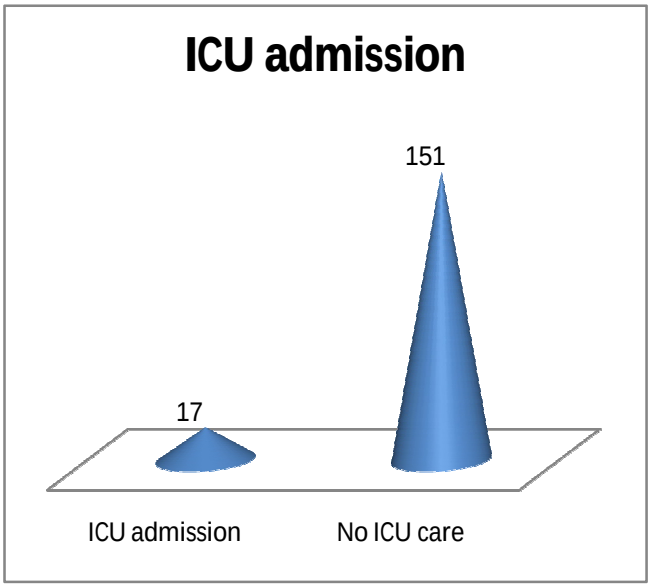
Figure 7- Severity of illness in the study population

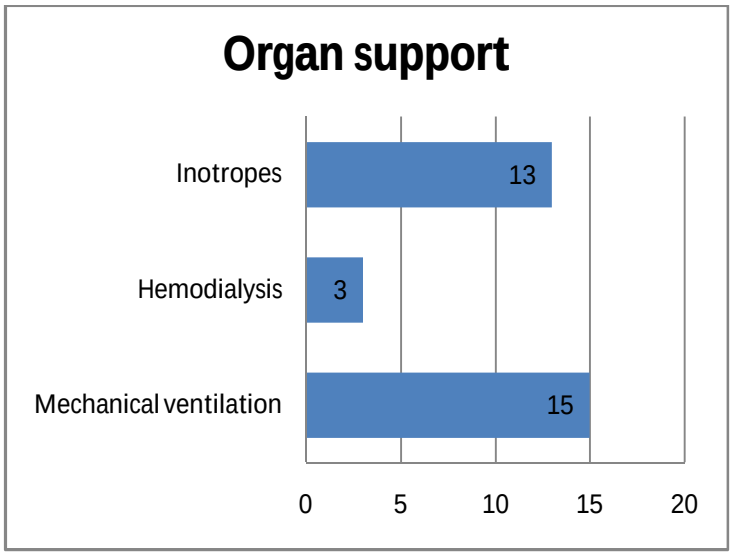


ICU stay and organ support

During the course of hospital stay, seventeen patients(10.1%) required admission in the intensive care unit. The commonest reason for ICU admission was acute lung injury. Fifteen patients required mechanical ventilatory support. Of these, fourteen patients required invasive mechanical ventilation and one patient required noninvasive ventilation. Thirteeen patients required inotropic support. Three patients underwent hemodialysis during their stay in the ICU. The duration of hospital stay ranged from 1 to 46 days. The median duration of ICU stay was nine days.

Figure 8 - ICU admission and organ support in the study population





Surgery and other interventions

Surgical necrosectomy was done in one patient during the course of our study. Three patients underwent endoscopic necrosectomy. Endoscopic ultrasound guided pseudocyst drainage was done in four patients. Eleven patients had ultrasound/CT guided drainage procedure for infected collections/ necrosis. One patient with a jejunal artery pseudoaneurysm, who presented with a massive GI bleed underwent interventional radiology guided coil embolization of the pseudoaneurysm. Nine patients underwent ERCP owing to associated cholangitis.

In sixty two (36.9%) patients, a nasojejunal tube was placed for early enteral nutrition. Seven patients with severe disease expired during the initial days of admission while they were still on intravenous fluids. The rest of the patients were started on oral diet once their pain settled. None of the patients in our series were given total parenteral nutrition.

Figure 9- Interventions in the study population

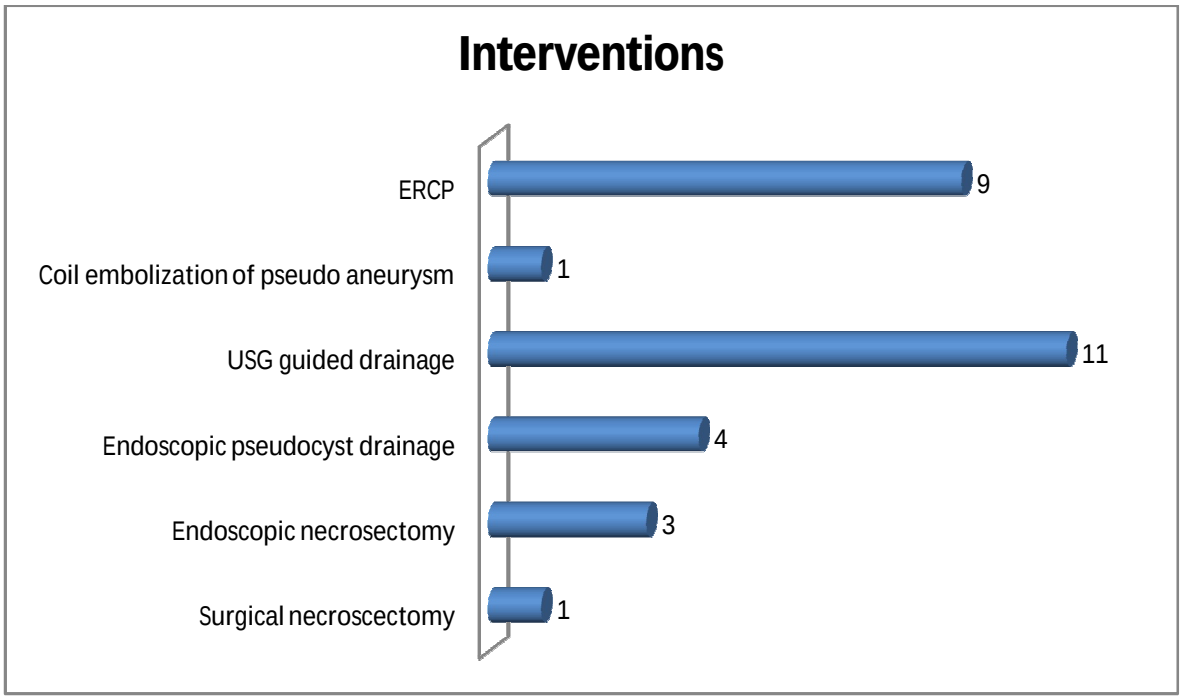
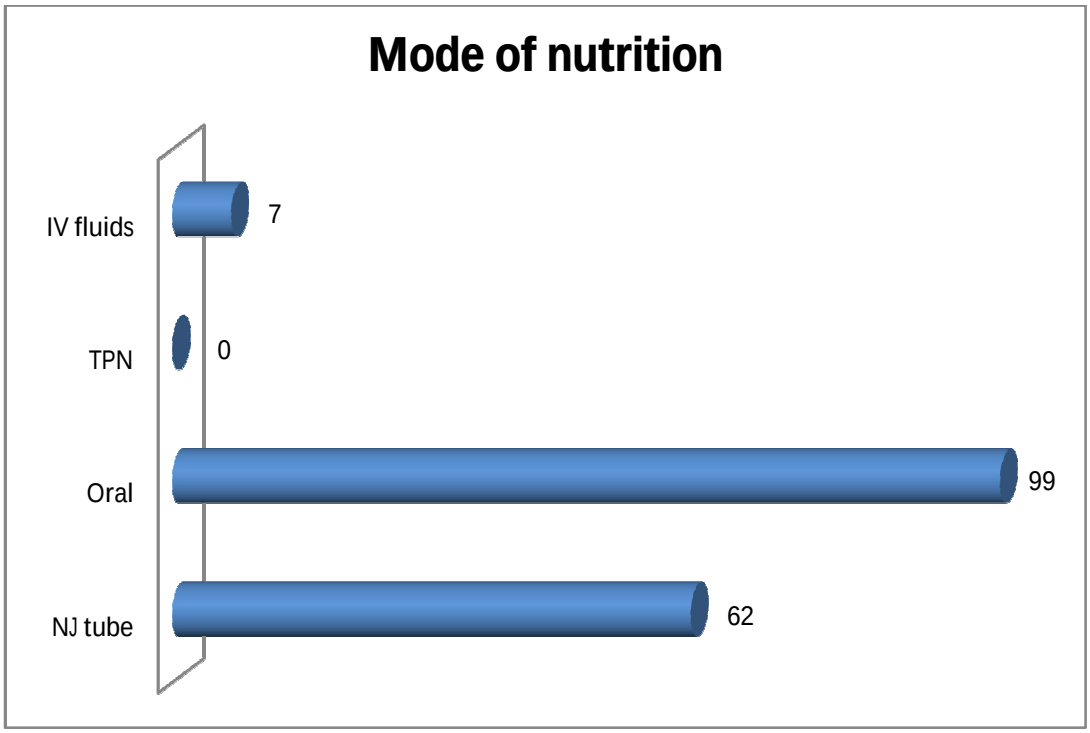


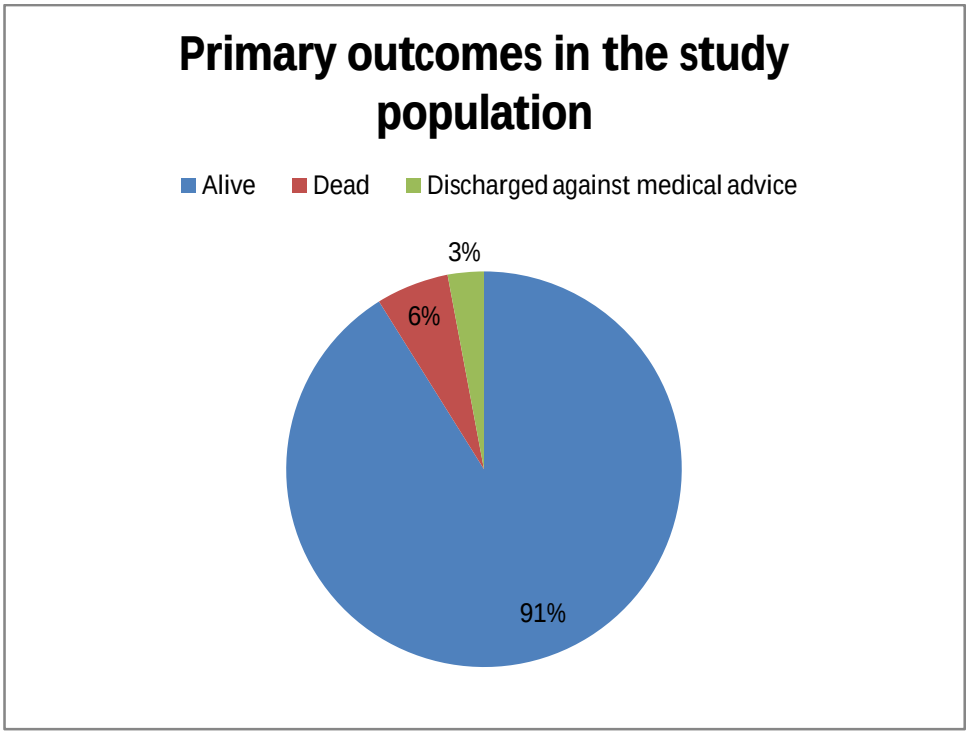
Figure 10- The mode of nutrition in the study patients



Mortality in the study population

One hundred and sixty eight patients with acute pancreatitis were enrolled in our study. Ten patients (5.95%) expired during the hospital stay. Five patients (2.97%) were discharged against medical advice in a very serious condition. One hundred and fifty three patients were discharged alive in a stable condition. Of the ten patients who died in hospital, eight of the died within eight days of admission secondary to complications of SIRS. The remaining two patients died after twenty three and thirty three days of admission respectively, secondary to infectious complications and sepsis. Four of the five patients who were discharged against medical advice left at least after two weeks of admission. One patient left against medical purpose on the eight day of admission. For the purpose of analysis, the patients who left against medical advice are also classified as dead owing to their moribund status.

Figure 11- Primary outcome in the study population



Genetic analysis

DNA extraction and genetic analysis were successful in all 168 patients. The allele frequencies for all the three major polymorphisms were determined. The results were in Hardy –Weinberg equilibrium except the TNF 308 polymorphism. The differences in the distribution of genotypes between mild and severe cases, patients with local complications and those without, patients with systemic complications and those without, patients who required ICU stay and those who did not & patients who died due to the illness and those who survived were analyzed.

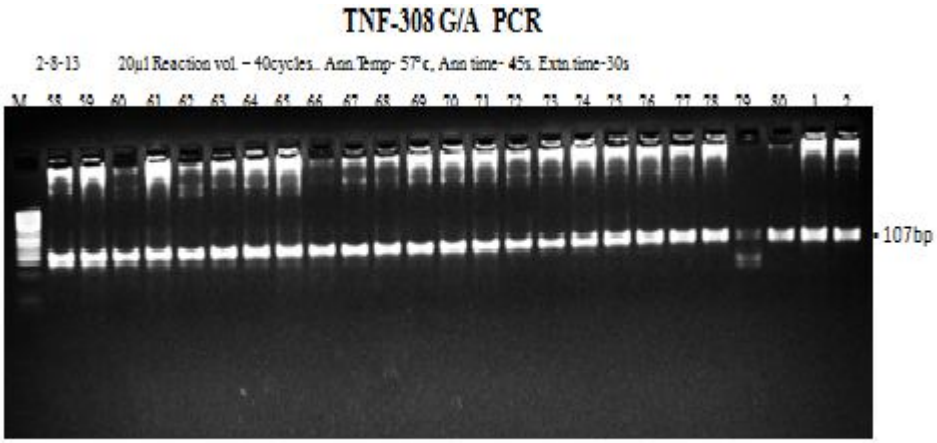


Figure 12- TNF-308G/A PCR

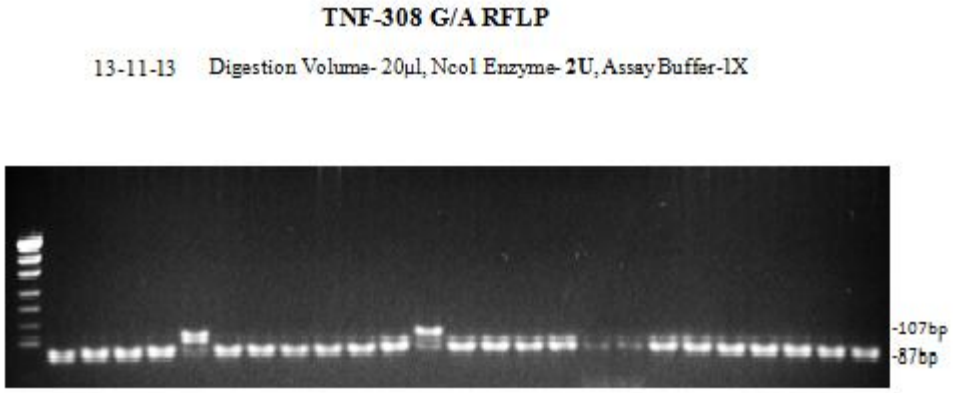


Figure 13- TNF 308 G/A RFLP

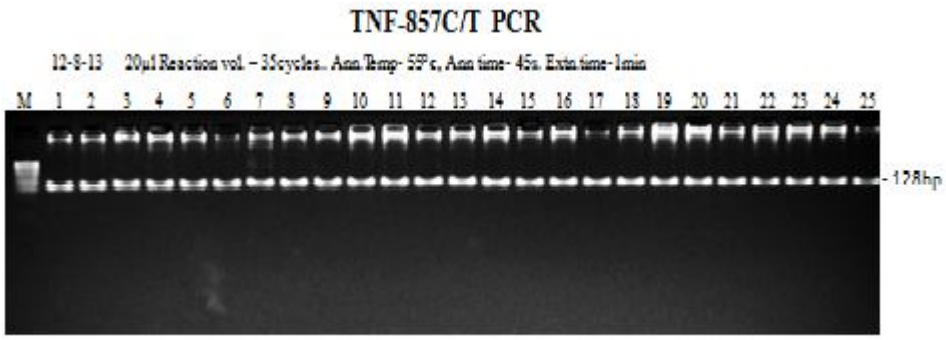


Figure 14- TNF 857 C/T PCR

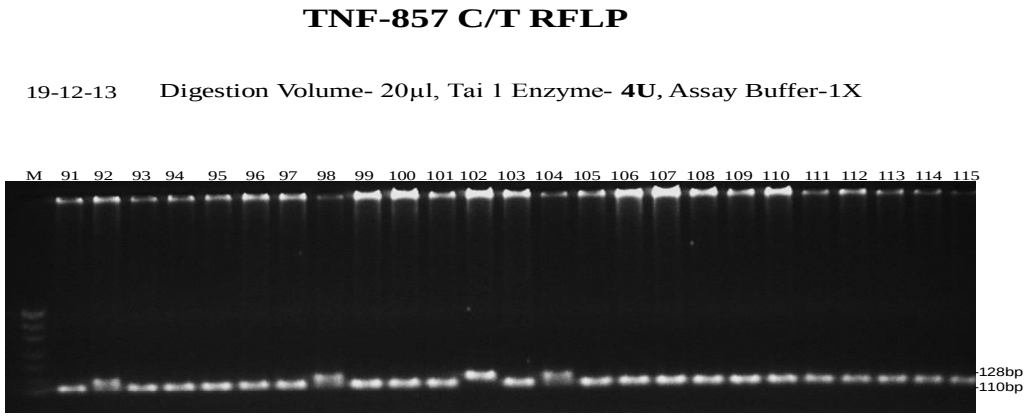


Figure 15- TNF 857 C/T RFLP

TNF-863 C/A PCR

25-7-13 20µl Reaction vol. – 35cycles.. Ann.Temp- **56°c,** Ann time- 30s

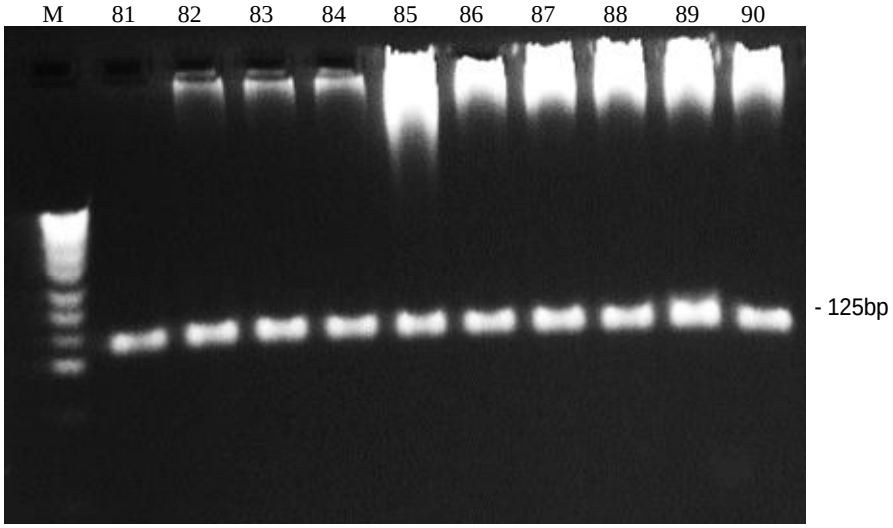


Figure 16 TNF -863 C/A PCR

TNF-863 C/A RFLP

6-11-13 Digestion Volume- 20µl, Tail Enzyme- 4U, Assay Buffer-1X

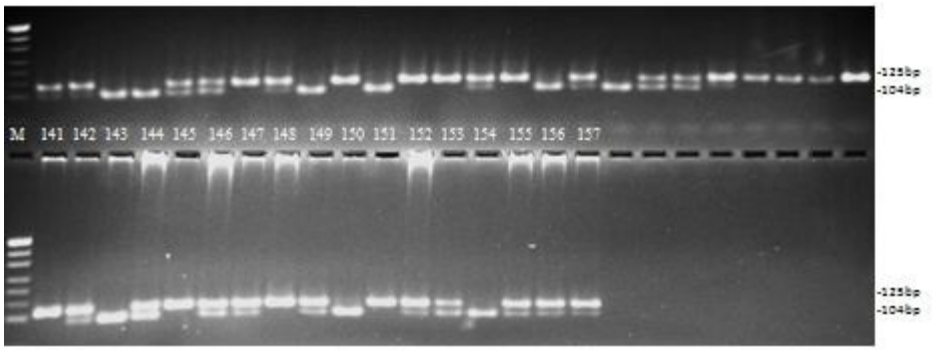


Figure 17- TNF 863 C/A RFLP

Table 7- TNF 308 polymorphisms and outcomes

COMPLICATION	OUTCOME	GA	GG	P VALUE
Local complication	Absent	4	92	0.72
	Present	4	68	
Systemic complication	Absent	4	96	0.71
	Present	4	64	
Severity	Mild	3	70	1.00
	Severe	5	90	
ICU stay	No	8	143	1.00
	Yes	0	17	
Outcome	Alive	8	145	1.00
	Dead	0	15	

Table 7 shows the distribution of TNF 308 genotypes. The AA genotype was absent in our study population. The distribution of genotypes was compared against various outcomes of pancreatitis like local complications, systemic complications, severity of illness, the need for ICU stay and mortality by Fischer exact test. The parameters studied did not show any statistically significant association with the inflammatory genotype GA. More over the distribution of TNF 308 genotypes did not satisfy the Hardy –Weinberg equilibrium.

Table 8- TNF-857 polymorphisms and outcomes

COMPLICATION	OUTCOME	CC	CT	TT	P VALUE
Local complication	Absent	83	11	2	0.01
	Present	50	21	1	
Systemic complication	Absent	84	13	3	0.02
	Present	49	19	0	
Severity	Mild	64	7	2	0.01
	Severe	69	25	1	
ICU stay	No	121	27	3	0.45
	Yes	12	5	0	
Outcome	Alive	122	28	3	0.64
	Dead	11	4	0	

Table 8 shows the distribution of TNF 857 genotypes. The association of the CT and TT genotypes with the outcomes of pancreatitis like local comlications, systemic complications, severity of illness, the need for ICU stay and mortality was studied by Chi square test. Local complications, systemic complications, and severity of illness showed a statistically significant association with the CT and TT genotypes. However mortality and the need for ICU admission did not show this association.

Table 9- TNF-863 polymorphisms and outcomes

COMPLICATION	OUTCOME	AA	CA	CC	P VALUE
Local complications	Absent	15	20	61	0.23
	Present	8	23	41	
Systemic complications	Absent	14	21	65	0.24
	Present	9	22	37	
Severity	Mild	12	14	47	0.21
	Severe	11	29	55	
ICU stay	No	20	39	92	0.87
	Yes	3	4	10	
Outcome	Alive	21	41	91	0.49
	Dead	2	2	11	

Table 9 shows the distribution of TNF 863 genotypes. The distribution was in Hardy – Weinberg equilibrium. The association of the AA and CA genotypes with the outcomes of pancreatitis was assessed by Chi square test. The studied parameters did not show a statistically significant association with the inflammatory genotypes.

DISCUSSION

Study population

Our study included all patients with acute pancreatitis. No age group was excluded from our study. Four percent of our patients were less than eighteen years of age and nineteen percent of the patients were more than fifty five years of age. Some studies in the past have excluded patients more than 75 years of age[69]. de-Madaria et al have excluded patients less than eighteen years of age in their study[71].

Ourcriteria for the diagnosis of acute pancreatitis was similar to almost all previous studies. Our study population consisted of a heterogenous group of patients with all etiologies of acute pancreatitis included for the study. Most of the studies in the past have also included all etiologies of acute pancreatitis. However, Zhang et al included only patients with biliary pancreatitis which was a more homogenous study population[69]. Moreover this study also included only those patients with first attack of acute pancreatitis. Our study included patients with recurrent attacks of acute pancreatitis provided they were not known to have underlying chronic pancreatitis. After inclusion, if a further imaging in hospital showed evidence of chronic pancreatitis, those patients were excluded. In our study eleven patients were excluded after initial inclusion since further imaging during the hospital stay showed evidence of chronic pancreatitis. Some investigators like Tukiainenet al have excluded those patients with more than three episodes of acute pancreatitis, due to the possibility of underlying chronic pancreatitis[70]. We have included patients with recurrent attacks even when the number of attacks were>5 times when there was no evidence of chronic pancreatitis. However in our patients, a CT scan was done only when the clinician suspected a complication of acute pancreatitis. An imaging at admission was not done in any of our patients, even in those with recurrent attacks, to ruleout chronic pancreatitis. So it is possible that few of our study

patients might have underlying chronic pancreatitis.Most of the other studies on TNF polymorphisms have also included patients with recurrent attacks. Zhang et al included only those patients who presented to hospital within 36 hours of the onset of pain[69]. de-Madariaet al have excluded those patients who presented after 48 hours of the onset of pain[71]. In both these studies serum levels of cytokines were also measured in addition to the genotype determination. Since our study did not involve cytokine measurements, we included patients with acute pancreatitis regardless of the time duration between the onset of pain and the presentation to hospital.

The mean age of our study population was 40.55± 15.02 years. Our study population was about a decade younger than most other published studies. The mean age in the study population of Ozhan et al was 52.7±15.1 years[72]. The median age of the patients in the study by Tukiainen et al was 51 years[70]. In the study by Powell et al, the median age of the patients with mild pancreatitis group was 51 years and the median age of the patients in the severe pancreatitis group was 57 years.

In our study, alcohol was the most common etiology accounting for 46.4 percent of the cases. Gallstones were the cause of acute pancreatitis in only 17.8 percent of our patients. The study by Zhang et al included patients with only biliary pancreatitis. In the studies by Tukiainenet al and Baloget al, alcohol was the most common etiology of acute pancreatitis, accounting for 61 percent and 44.15 percent respectively[70,9]. However, in the studies by de-Madaria et al and Powell et al, gall stones were the predominant cause of acute pancreatitis, accounting for 61 percent and 42.63 percent of the cases respectively[71,68]. A large proportion of our cases were idiopathic(25%). We have classified them as idiopathic after excluding all the known causes of acute pancreatitis. Other series have also reported idiopathic cases but in

relatively small numbers. In the study by Powell et al; out of the total 190 patients studied, thirty patients(15.7%) were classified as idiopathic. de-Madaria et al have reported that 18% of their patients with acute pancreatitis were idiopathic. Balog et al have reported that 10.3% of patients in their study had no known etiology of acute pancreatitis. These patients were classified as idiopathic.

Complications and severity of illness

In our study we have classified any patient with a local or systemic complication as having a severe disease. We used the Atlanta 2012 classification to define the local and systemic complications. Although the Atlanta 2012 classification has a group called moderately severe pancreatitis, we clubbed the moderately severe and severe pancreatitis groups together as severe pancreatitis. Different studies in the past have used different criteria to assess the severity of illness. Tukiainen et al [70],de-Madaria et al[71] ,Ozhanet al [72],Powell et al[68] have used Atlanta 1992 classification to define severe pancreatitis. The classification of mild and severe pancreatitis in these studies is similar to our study. Zhang DL et al [69] have classified their patients into severe pancreatitis based on an APACHE score of ≥8 and a CTSI ≥4.Balog A et al [9] have classified all patients with acute pancreatitis as mild and severe based on the original criteria of Ranson. Any patient with a Ranson score of more than or equal to three were classified as having severe pancreatitis. This was one major study that reported a positive correlation between TNF 308G/A polymorphism and severity of acute pancreatitis. However it can be seen that the classification into severe disease in this study was not based on the development of local or systemic complications but based on a score at admission.

In our study, 57% of study population had severe disease while only 43% had a mild disease. This is contrary to the general expectation that two thirds of the patients with acute

pancreatitis have mild disease. This could be because of the fact that only those patients with severe disease could have been referred to our hospital, which is a tertiary referral centre. Other studies on acute pancreatitis have also reported similar results. Balog et al [9] reported that 62.3% of their patients with acute pancreatitis had severe disease. In the study by Zhang et al [69] severe pancreatitis accounted for 48.03% of cases with acute pancreatitis.

In our study 42.8%of the study population had one local complication or another. However it must be emphasized that a CT scan was done only in eighty three patients (49.4%) of the total study population since it was performed only when the treating physician suspected a local complication based on the clinical status of the patients. It might very well be possible that pancreatic necrosis and related complications could have been present in some patients who were relatively asymptomatic for whom a CT scan was not considered. We did not have a predefined set of criteria prior to ordering for CT. In the study by de-Madaria et al,[71] a CT scan was ordered in those patients who met any of the following criteria:

a. Presence of SIRS
b. Presence of organ failure
c. CRP >15 mg/dl
d. APACHE score>8

In that study fifteen out of eighty three patients had local complications of acute pancreatitis(18.07%). None of the studies on acute pancreatitis had CT scan done in all the patients.

The mortality from acute pancreatitis in our study was about 9%. Powell et al[68]have reported 22% mortality in severe pancreatitis and 2% mortality in mild pancreatitis in their study of 190 patients. de-Madaria et al[71] have reported two deaths in their study of eighty four patients

with acute pancreatitis. In the study by Tukiainen E et al[70] , of the 397 patients studied there were five deaths.

In our study eleven patients had proven bacteremia during the course of hospital stay. E.coli was the commonest organism isolated. Six patients met the criteria for infected pancreatic necrosis (either a positive culture on diagnostic aspirate or imaging evidence). Six patients had documented infected peripancreatic collections (diagnosed based on a positive culture from a diagnostic aspirate). Balog et al [9]reported that twenty percent of their patients with acute pancreatitis had infected pancreatic necrosis. Tukiainen et al[70] have reported that infectious complications developed in forty seven patients of a total of 397 patients studied.

Genetic analysis

Our study showed a significant association between TNF 857C/T polymorphisms and the severity of acute pancreatitis. Both the local and systemic complications of acute pancreatitis were significantly associated with this polymorphism. However the study did not show a statistically significant association of this polymorphism with the need for ICU stay or mortality in our population. This could probably be because of the fact that the number of patients in both these groups were low. Only seventeen patients in our study population required ICU stay and only fifteen patients died (ten patients who expired in hospital and five patients who were discharged against medical advice).

Ours was not the first study on the association between TNF 857C/T polymorphisms and the severity of acute pancreatitis. In 2012Bishehsari et al had studied 211 patients with acute pancreatitis and 401controls.[73]In this study there was no significant difference in the distribution of TNF 857 genotypes between the cases and controls. Moreover the study did

not show a significant association between TNF 857 C/T polymorphisms and the outcomes of acute pancreatitis. No other group has studied TNF 857 C/T polymorphisms in acute pancreatitis before this. Our study is the first to report a positive association between TNF 857C/T polymorphisms and the outcomes of acute pancreatitis.

Almost every study in the past while evaluating the association between the outcomes of acute pancreatitis and TNF polymorphisms had a control group. The aim of having this control group was to study if the TNF polymorphisms predispose the carriers of these mutant allelles to acute pancreatitis. However none of these past studies showed a difference in the distribution of TNF genotypes between the cases and controls. Our study did not have a control group. Our hypothesis was that TNF polymorphisms could have a modifier effect on acute pancreatitis, that is these polymorphisms as such do not cause acute pancreatitis, however if a patient developed acute pancreatitis, they affect the severity of acute pancreatitis. Our hypothesis was in accordance with data from animal studies which have conclusively shown that high cytokine levels alone cannot initiate acute pancreatitis. Perfusion of the isolated human pancreas with high doses of IL-1 and TNF have shown little evidence that these agents can initiate an attack of acute pancreatitis[49]. The modifier effect of TNF levels is further demonstrated by studies in gene knockout animals. When acute pancreatitis is induced in animals devoid of IL-1 or TNF receptors, they fail to develop maximal pancreatitis[50].Pancreatitis does develop in these transgenic animals, yet its severity/lethality never reaches that of wild-type mice. These studies thereby establish that pancreatitis is not initiated or triggered by 1L-1 or TNF, however they both play an important role in its progression. So in our study the mild and severe groups of pancreatitis were compared against each other.

These polymorphisms studied are in the promoter region of the TNF alpha gene. Past studies have proven that polymorphisms in the TNF alpha gene are associated with increased levels of TNF alpha production[57,58,59]. So it might be possible that such genetically determined differences in the level of this key cytokine might affect the progression of disease and outcome in acute pancreatitis once an acute insult has initiated the injury. This also might explain the individual differences in disease severity in patients suffering the same initial insult.

TNF alpha levels

If the disease severity in acute pancreatitis is modified by the levels of inflammatory cytokines, it appears logical that measuring blood levels of TNF alpha might serve as a prognostic marker in acute pancreatitis. Zhang et al from China[69]studied the TNF 308 polymorphisms in 127 patients and 102 healthy controls with acute pancreatitis. They measured TNF alpha levels in all patients of acute pancreatitis at admission. Among the 61 patients with severe pancreatitis in that study, TNF alpha levels at admission were similar in those patients who developed septic shock and those who did not. There was no significant correlation between the TNF alpha- 308 polymorphisms and plasma TNF alpha levels at admission in the patients studied. In 2008 de-Madaria et al studied TNF-238 polymorphisms, TNF alpha-308 polymorphisms and cytokine levels in patients with acute pancreatitis. In this study also, blood for genetic analysis and cytokine levels were collected at admission. Both the polymorphisms studied did not show any correlation with the cytokine levels in the patients studied.

The studies on TNF levels, TNF gene polymorphism and severity of disease in acute pancreatitis have not shown any positive correlation with TNF levels and the severity of

illness. This could be because of numerous reasons. The blood sample for cytokine levels in all the studies is collected at admission. However different patients present at different times to the hospital after the onset of illness. Studies on experimental models of acute pancreatitis have shown that the concentration of TNF and IL-1 within pancreatic tissues was substantially higher than the serum levels[44]. It might be that the tissue levels of TNF alpha are more important in the pathogenesis of acute pancreatitis than the serum levels. The direct measurement of these cytokines in blood is often erratic in view of the intermittent nature of secretion, low half life of cytokines in circulation and clearance by the liver[42]. So if the disease severity can be positively correlated to a genetic polymorphism, that might serve as an excellent prognostic marker.

TNF 308 G/A is the most widely studied polymorphism in the setting of acute pancreatitis. Our study did not show any association between TNF 308G/A polymorphisms and severity of disease in acute pancreatitis. Moreover the distribution of TNF genotypes did not satisfy the Hardy –Weinberg equilibrium. This was probably related to the absence of AA genotype in our study population. Of the 168 patients studied 160 had GG genotype and eight patients had GA genotype. Unpublished, population based data from our department had shown that the frequency of GA and AA genotypes in south Indian population is about eight percent. However the frequency in our study population was found to be different. The reason for this difference is not clear.

In the study by Powell et al there were 190 patients with acute pancreatitis[68]. Of these 113 patients had mild disease and 77 patients had severe disease. The study did not show a positive correlation with TNF polymorphisms and the severity of disease. The study by Zhang et al from China[69]also did not show a positive correlation between TNF 308 G/A

polymorphisms and outcomes of acute pancreatitis. This study had a total of 127 patients, sixty one patients with severe pancreatitis and the rest with mild disease. This study however found a significant difference in the TNF alpha- 308 polymorphism distribution when comparing patients with and without septic shock.TNF2 was found in 50 % of patients who developed septic shock compared with 20.1 %of patients with no septic shock (odds ratio-5.155, *P*=0.023). However in our study there was no association between TNF 308 G/A polymorphism with any of the systemic complications of pancreatitis, including hypotension.
In a prospective single centre trial from Hungary, Balog A et al reported that the GA genotype was more common in patients with severe pancreatitis compared to those with mild disease with an odds ratio of 3.145. The number of homozygotes for the inflammatory allele (AA genotype) was very low in this study similar to our study(2 out of 77 patients). In one of the largest studies on TNF 308G/A polymorphisms in acute pancreatitis, Tukiainen etalstudied 397 patients with acute pancreatitis. The study failed to show any association between TNF 308 G/A polymorphisms and the outcomes and severity of acute pancreatitis. The study by de-Madaria et al published in 2008, also did not show any correlation between TNF genotypes and outcomes of acute pancreatitis.

TNF 863 C/A polymorphism and the outcomes of pancreatitis was studied by Bishehsariet al in the past. They found that the A allele was associated with an increased risk of progresssion to multiorgan dysfunction syndrome. However our study did not show any such association. Moreover the TNF 863 C/A polymorphism was not associated with any of the local complications or systemic complications of acute pancreatitis in our study.

Limitations of our study

Being a tertiary referral centre, referral bias is an important limitation. Chronic pancreatitis was not excluded by imaging in all our patients. A CT scan was done only in eighty three patients (49.4%) of the total study population. Due to the same reasons we could have missed a few local complications of acute pancreatitis. Our sample size calculation was based on the assumption that two thirds of the patients with acute pancreatitis will have mild acute pancreatitis and one third will have severe disease. However in our study population only 43% had mild disease and 57% had severe disease. The distribution of TNF 308 G/A genotypes in our study population did not satisfy the Hardy –Weinberg equilibrium.

The future implications

If future studies also prove that the severity of disease and outcomes in acute pancreatitis show a positive correlation with TNF 857 C/T polymorphisms, this test can serve as an excellent prognostic marker and predictor of severity in patients with acute pancreatitis. This might help us to prioritize patients and plan early ICU admission in those who are likely to deteriorate. Unlike the cytokine levels which tend to vary with time, this test being a genetic test can be done at any time since the results do not change with time.

SUMMARY AND CONCLUSIONS

1. Alcohol was the commonest etiology of acute pancreatitis in our study population
2. 82% of our patients were males
3. 76.7% of our patients were in the age group 18-55 years
4. 42.8% of the patients had a local complication
5. Acute fluid collection was the commonest local complication
6. 14.2% of patients had a vascular complication secondary to acute pancreatitis
7. 40.4% patients had a systemic complication of pancreatitis
8. Acute lung injury was the commonest systemic complication
9. Six patients had proven infected pancreatic necrosis
10. 17.2% of patients had recurrent attacks of acute pancreatitis
11. 43% of patients had mild acute pancreatitis while 57% of patients had severe acute pancreatitis
12. 10.1% of our patients were admitted in the ICU
13. The mortality in our study population was 8.9%
14. The local complications, systemic complications and severity of illness in acute pancreatitis showed a positive correlation with TNF 857C/T polymorphism
15. The other polymorphisms studied did not show any correlation with the outcomes of acute pancreatitis

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APPENDIX

Informed Consent document &PATIENT'S INFORMATION

I understand that Dr. JIFFY RASAK .V.A is doing a study to identify the parameters that help in correlating the severity of acute pancreatitis and gene polymorphism. The study involves being interviewed (about the disease) and noting the results of test reports that are being done by the treating doctors for clinical care. A sample of blood will be taken to find out if there is a particular kind of gene pattern that may predispose me (or my patient) to severe illness. The results of the test done in connection with the study may not directly benefit me. They are likely to indirectly benefit other patients with the disease.

I understand that my withdrawal from the study at any time will not affect the treatment being given.

Study Title: Study Number:
Subject's Initials: _____ Subject's Name: _____
Date of Birth / Age:_____ Please initial box
(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]
(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]
(iii) I understand that my identity will not be revealed in any information released to third parties or published. [ ]
(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]
(v) I agree to take part in the above study. [ ]
(vi)I also give consent to use the blood samples for further studies , provided such a use is only for scientific purpose and without disclosure of personal information.
(vii) I understand that i can contact the investigator at 8220249723 at any time for further clarification regarding the study

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____ Date: _____/_____/_____
Signatory's Name: _____

Signature of the Investigator: _____
Date: _____/_____/_____
Study Investigator's Name: _____

Signature of the Witness: _____
Date:_____/_____/_____
Name of the Witness: _____

PROFORMA Study no.

Demographic data

Name :
Age (years) :
Sex : Male / Female
Hosp Num :
Occupation :
Address :

Phone No :

Recruitment data

Outpatient follow-up / Emergency Service / Admitted to ward

Clinical data

Abdominal pain: Duration:
Location: Epigastrium / Generalized / Other
Precipitating factors: Alcohol binge / Fatty food / Trauma / Others / Nil
Vomiting: Yes / No
Breathlessness: Yes / No
Decreased urine output: Yes / No
GI bleed: Yes / No
Fever: Yes / No
Others:
Alcohol consumption: Nil / Social / Alcoholic Qty Type Yrs

Admission characteristics:

Pulse BP Temp Respiratory rate

Simplified Glasgow scoring system (Score >2 in first 48 h = severe)

Variable	Absent	Present
Age >55 yrs		
PaO_2 <60 mm Hg		
WBC >15,000/mm^3		
Ca^{2+} (uncorr.) <8 mg%		
LDH >600 IU/L		
Glucose >180 mg%		
Urea >45 mg%		
Albumin <3.2 g%		
TOTAL SCORE		

CRP :
S. Amylase :
S. Lipase :
PCV :

Chest X Ray: Normal Y / N (if abnormal, at admission or later?)
Effusion Y / N
ARDS Y / N

Ultrasonography:
Gallstones / Biliary dilatation / Pancreatic oedema / Fluid collection / Other

CECT: Done / Not done CTSI (if available:

Findings:

Hospital course:
Admitted during study / Discharged from A&E / Date obtained from records
(now seen in OPD)

I) ***Local complication***: Acute fluid collection
Pseudocyst
Abscess

II) ***Organ Failure***: Yes / No
CVS Systolic BP <90 mm Hg
Respiratory PaO_2 <60 mmHg
Renal Creatinine >2 mg/dl after rehydration
Haematologic GI Bleed >500cc in 24 hours
CNS
Liver

III) ***Sepsis***:

Hospital stay: ____ days DOA DOD

ICU stay: No / Yes If yes, ____ days

Interventions:
Pressor support needed N / Y
Ventilatory support needed N / Y (non-invasive / invasive)
Dialysis support needed N / Y

Feeding: TPN / NJ / Oral
Surgery: Yes / No
Outcome: Dead / Alive

Final Diagnosis: Acute pancreatitis (first attack)
Aetiology :
Severity :

SL.NO	HOSP. NO	AGE	SEX	TNF 308	TNF 857	TNF 863	STATE	OCCUPATION	COMORBIDITIES	PRESENTATION	ADMISSION	PAIN	DURATION	VOMITING	BREATHLESSNESS	OLIGURIA	FEVER	ALCHOHOLIC	SGS SCORE	SGS >2	CRP
1	846266D	30	1	GG	CC	CC	1	LABOURER	0	1	0	1	2	1	0	0	0	1	0	0	7.6
2	273703F	41	0	GG	CT	CA	2	HOUSE WIFE	0	1	1	1	3	1	0	1	0	0	5	1	168
3	287429F	39	1	GG	CC	CC	3	LABOURER	0	1	0	1	14	1	1	0	0	1	3	1	106
4	270969F	11	0	GG	CC	CC	4	STUDENT	0	1	1	1	3	1	0	0	0	0	0	0	6.6
5	265661D	51	1	GG	CT	CC	5	INSURANCE	0	1	1	1	10	1	0	0	0	1	1	0	92.7
6	291368F	31	1	GG	CC	CC	2	LABOURER	0	1	1	1	4	1	0	0	0	1	4	1	87
7	291698F	37	1	GG	CC	CC	1	BUSINESS	0	1	0	1	3	1	0	0	0	1	2	0	16
8	295458F	50	1	GG	CC	AA	5	PVT.JOB	1	2	1	1	45	1	1	0	0	0	4	1	8
9	452733B	16	1	GG	CC	CC	2	STUDENT	0	1	1	1	2	1	0	0	0	0	0	0	15
10	546009C	73	1	GG	CT	CC	2	RETIRED	1	1	1	1	1	1	0	0	0	0	3	1	33
11	194104F	43	1	GG	CC	CC	2	DRIVER	2	1	1	1	2	1	0	0	0	0	0	0	63
12	299207F	65	1	GG	CC	CC	2	RETIRED	3	1	1	1	2	1	0	0	0	0	3	1	88
13	475666A	28	1	GG	CC	CC	2	STUDENT	0	1	1	1	1	0	0	0	0	0	1	0	18
14	281093F	19	1	GG	CT	CA	5	STUDENT	0	1	1	1	2	1	0	0	0	0	0	0	16
15	261029F	32	1	GA	CC	CC	6	BUSINESS	0	2	1	1	60	0	1	0	0	1	3	1	91
16	730034C	63	1	GG	CC	CC	6	RETIRED	0	1	1	1	3	1	0	0	0	0	1	0	8
17	186660F	25	1	GG	CC	CA	5	LABOURER	0	1	1	1	3	1	0	0	0	0	0	0	16
18	313206F	29	1	GG	CC	CC	2	LABOURER	0	1	1	1	10	1	0	0	0	1	4	1	206
19	309557F	48	1	GG	CC	CC	1	PVT.JOB	0	1	1	1	4	1	0	0	0	1	6	1	174
20	309641F	29	1	GG	CC	CC	1	LABOURER	0	1	1	1	4	1	1	0	0	0	2	0	115
21	317233F	39	1	GG	CT	CC	2	BUSINESS	0	1	1	1	2	1	0	0	0	0	1	0	8.5
22	625181D	52	1	GG	CT	CC	4	BUSINESS	1	1	1	1	4	1	0	0	0	1	1	0	188
23	310081F	21	1	GG	CC	AA	5	STUDENT	0	1	1	1	2	1	0	0	0	0	0	0	34
24	338538F	32	1	GG	CC	CC	2	LABOURER	0	1	1	1	5	1	0	0	1	0	0	0	131
25	342730F	44	1	GG	CC	CC	5	HOUSE WIFE	0	1	1	1	5	1	0	0	0	0	1	0	6.9
26	316672F	29	1	GG	CC	CC	1	BUSINESS	0	2	1	1	30	1	1	0	1	1	6	1	181
27	331532F	61	1	GG	CC	CC	1	RETIRED	4	1	1	1	1	1	1	0	0	0	5	1	212
28	061735A	50	1	GG	CC	CC	2	CMC	4	1	1	1	1	1	0	0	0	1	1	0	17.1
29	341916F	42	1	GG	TT	CC	1	BUSINESS	1	1	1	1	2	1	0	0	0	1	0	0	137
30	350399F	34	1	GG	CC	CC	2	LABOURER	1	1	1	1	6	1	1	0	0	1	4	1	189
31	379724F	39	1	GG	CT	CC	1	PVT.JOB	2	1	0	1	3	1	1	0	0	0	3	1	115
32	475410C	58	1	GG	CC	CC	2	LABOURER	4	1	1	1	5	1	0	0	0	0	4	1	250
33	290269F	37	1	GG	CC	CC	2	MECHANIC	1	1	1	1	3	1	0	0	0	0	1	0	65.6
34	863110D	24	1	GG	CC	CC	2	LABOURER	0	1	1	1	5	1	1	0	1	1	3	1	204
35	374526F	36	1	GG	CT	CC	2	DRIVER	4	1	1	1	6	1	0	0	0	1	3	1	154
36	317925F	28	1	GG	CC	CC	2	SOCIAL WORKER	6	1	1	1	4	1	0	0	0	0	0	0	108
37	374333F	29	1	GG	CC	AA	1	LABOURER	0	1	1	1	4	1	1	0	1	1	5	1	206
38	367723F	59	0	GG	CC	AA	2	HOUSE WIFE	1	1	1	1	1	1	0	0	0	0	4	1	41
39	005245F	38	1	GG	CC	CC	1	SHOP KEEPER	0	1	1	1	2	1	0	0	0	1	0	0	51.3
40	373384A	65	1	GG	CC	CC	2	RETIRED	0	1	1	1	1	0	0	0	0	1	3	1	176
41	554522B	50	1	GG	CT	CA	2	LABOURER	1	1	1	1	3	1	0	0	0	1	3	1	204
42	315187F	49	1	GG	CC	CC	5	PVT.JOB	0	1	1	1	2	1	0	0	0	0	1	0	6
43	389154F	41	1	GG	CT	CA	1	ELECTRICIAN	0	1	1	1	5	1	1	0	0	1	3	1	204
44	379320F	33	0	GG	CC	AA	1	TEACHER	0	1	1	1	2	1	0	0	0	0	1	0	95
45	373239F	66	0	GG	CC	CC	2	HOUSE WIFE	4	1	1	1	3	1	0	0	0	0	1	0	12.4
46	361242F	40	1	GG	CT	CC	2	LABOURER	0	1	1	1	5	1	0	0	0	0	2	1	45
47	246773F	26	1	GG	TT	CC	2	PVT.JOB	0	1	1	1	2	1	0	0	0	1	0	0	114
48	309901F	23	1	GG	CT	CC	2	STUDENT	0	1	1	1	1	1	0	0	0	0	2	0	16.6
49	394317F	59	1	GG	CC	CC	1	RETIRED	3	1	1	1	2	1	0	0	0	1	1	0	106
50	674160C	78	1	GG	CC	CC	2	RETIRED	1	1	1	1	2	0	0	0	0	0	1	0	48.5
51	013331F	52	1	GG	CC	CC	1	HOUSE WIFE	7	1	1	1	2	1	0	0	0	0	2	0	76.2
52	401398F	66	1	GG	CC	CC	1	RETIRED	1	1	1	1	1	1	0	0	0	0	2	0	76.9
53	401469F	26	1	GG	CC	CC	1	FINANCIER	8	1	1	1	4	1	1	0	0	1	1	0	204
54	401388F	49	1	GG	CC	AA	2	ACCOUNTANT	3	1	1	1	5	0	0	0	0	0	2	0	204
55	379541F	21	1	GG	CC	CC	2	HOUSE WIFE	0	1	1	1	3	0	0	0	0	0	0	0	29
56	273445F	25	0	GG	CC	CC	2	HOUSE WIFE	0	1	1	1	2	0	0	0	0	0	1	0	143
57	337421F	33	1	GG	CC	CC	6	BUSINESS	0	2	1	1	36	0	0	0	0	1	3	1	204
58	396429F	43	1	GG	CC	CC	6	PVT.JOB	0	2	1	35	0	0	0	0	0	1	3	1	168
59	406258F	46	1	GG	CC	CC	1	BUSINESS	3	1	1	1	3	1	0	0	0	0	3	1	167
60	406386F	30	1	GG	CC	CC	2	LABOURER	0	1	1	1	1	1	0	0	0	1	2	1	70.5
61	422613F	28	1	GG	CC	AA	1	BUSINESS	0	1	1	1	2	1	1	0	0	1	4	1	204
62	566953D	64	1	GG	CC	CA	5	BUSINESS	9	1	1	1	3	1	0	0	0	0	2	0	167
63	426145F	41	1	GG	CC	AA	6	HOUSE WIFE	0	1	1	1	1	1	0	0	0	0	0	0	86
64	422515F	32	1	GG	CT	CC	2	MECHANIC	1	1	1	1	1	1	1	0	0	0	3	1	204
65	431386F	55	0	GG	CC	AA	5	HOUSE WIFE	10	1	1	1	15	1	0	0	0	0	1	0	11
66	434580F	61	1	GG	CC	CC	2	RETIRED	4	1	1	1	2	1	0	0	0	1	2	0	99.7
67	434625F	34	1	GG	CC	CC	1	PVT.JOB	0	1	1	1	4	1	0	0	0	1	1	0	12.8
68	434615F	31	1	GG	CC	CC	1	BUSINESS	0	1	1	1	2	1	1	1	0	1	3	1	206
69	441582F	35	1	GG	CC	CC	5	BUSINESS	0	1	1	1	3	0	0	0	1	1	3	1	76.7
70	448492F	71	1	GG	CC	AA	2	RETIRED	9	1	1	1	5	0	0	0	0	1	3	1	124

71	455700F	34	1	GG	CC	CA	1	BUSINESS	0	1	1	1	2	1	0	0	0	1	2	0	129
72	455371F	46	1	GG	CC	CA	1	LABOURER	0	1	1	1	5	1	1	0	0	1	5	1	206
73	455941F	35	1	GA	CC	CA	2	LABOURER	0	1	1	1	3	1	0	0	0	1	2	0	204
74	471690F	39	1	GG	CC	CA	5	BUSINESS	0	2	1	1	30	1	0	0	0	0	0	0	125
75	937754F	58	0	GG	CT	CC	2	HOUSE WIFE	1	1	1	1	4	1	0	0	0	0	3	1	60.5
76	474239F	35	1	GG	CC	CC	1	BUSINESS	0	1	1	1	10	1	0	0	0	1	2	1	204
77	458968F	21	1	GG	CC	CC	7	STUDENT	0	1	1	1	2	1	0	0	0	0	1	0	39.9
78	072576F	25	0	GG	CC	CC	2	HOUSE WIFE	0	1	1	1	3	1	0	0	0	0	0	0	5
79	473374F	28	1	GG	CC	CC	1	PVT.JOB	0	1	1	1	4	1	0	0	0	1	3	1	204
80	703980S	39	1	GG	TT	CC	2	PVT.JOB	1	1	1	1	2	1	0	0	0	1	2	0	67
81	476087F	51	0	GG	CC	CC	2	HOUSE WIFE	0	1	1	1	3	1	0	1	0	0	5	1	184
82	476410F	39	1	GG	CC	CC	2	LABOURER	0	1	1	1	4	1	0	0	0	1	5	1	204
83	485922F	36	1	GG	CC	CC	2	LABOURER	0	1	1	1	3	1	0	0	0	1	2	0	204
84	797188C	41	0	GG	CC	CC	2	HOUSE WIFE	0	1	1	1	5	0	0	0	0	0	0	0	78.8
85	396269B	17	1	GG	CC	CC	2	STUDENT	0	1	1	1	3	1	0	0	0	0	0	0	16
86	604499F	41	1	GA	CC	CC	1	COMPUTER OPERATER	0	1	1	1	3	1	0	0	0	0	0	0	188
87	612254F	35	1	GG	CC	CA	1	BUSINESS	3	1	1	1	20	1	0	0	0	1	0	0	44
88	620584D	31	1	GG	CC	CC	2	ARMY	0	1	1	1	3	1	0	0	0	1	2	0	204
89	490783F	43	1	GG	CT	CC	1	LABOURER	2	1	1	1	7	1	0	0	0	1	4	1	206
90	604965F	38	1	GG	CC	CC	2	FARMER	5	1	1	1	5	1	0	0	0	1	1	0	142
91	479777F	65	1	GG	CC	CA	8	HOUSE WIFE	5	1	1	1	1	1	0	0	0	0	1	0	78
92	582566D	23	1	GG	CC	CC	2	PVT.JOB	0	1	1	1	3	1	0	0	0	0	0	0	108
93	604570F	39	1	GG	CT	CA	2	BUSINESS	0	1	1	1	4	1	1	0	0	0	1	0	138
94	458975F	34	1	GG	CC	AA	2	LABOURER	0	2	1	1	30	0	0	0	0	1	1	0	59
95	611698F	23	1	GA	CC	CC	1	DRIVER	0	1	1	1	5	1	0	0	0	1	2	1	204
96	604983	58	0	GG	CC	CA	1	HOUSE WIFE	4	1	1	1	4	1	1	0	1	0	4	1	4.3
97	611660F	48	1	GG	CC	AA	2	PVT.JOB	8	1	1	1	2	1	1	0	0	0	4	1	34
98	623540F	36	1	GG	CC	CC	2	TEA SHOP	0	1	1	1	2	1	0	0	0	1	1	0	99
99	623505F	32	1	GG	CT	CC	2	LABOURER	0	1	1	1	4	1	0	0	1	1	2	1	204
100	415599F	32	1	GG	CC	CC	2	PVT.JOB	0	1	1	1	1	1	0	0	0	0	1	0	4.7
101	646551F	65	0	GG	CC	CA	2	HOUSE WIFE	1	1	1	1	3	1	0	0	0	0	2	0	168
102	789454C	31	0	GG	CC	AA	2	PVT.JOB	0	1	1	1	3	1	0	0	0	1	2	0	61
103	644169F	61	1	GG	CC	AA	5	RETIRED	3	1	1	1	8	1	0	0	0	0	2	0	104
104	639560F	35	1	GG	CC	CC	1	BUSINESS	0	2	1	1	3	1	1	0	0	0	3	1	204
105	341719F	46	1	GG	CC	CC	2	PVT.JOB	4	1	1	1	3	1	0	0	0	1	1	0	147
106	129335A	50	0	GG	CC	CC	2	HOUSE WIFE	4	1	1	1	1	1	0	0	1	0	1	0	167
107	623624F	47	0	GG	CC	CA	6	HOUSE WIFE	1	2	1	1	30	1	1	0	1	0	5	1	186
108	113085F	33	1	GA	CC	CA	2	LABOURER	0	1	1	1	3	1	0	0	0	1	2	0	204
109	651610F	38	0	GG	CC	CC	2	HOUSE WIFE	0	1	1	1	2	1	0	0	0	0	0	0	16
110	701361A	80	1	GG	CC	CA	2	RETIRED	9	1	1	1	2	1	0	0	0	0	4	1	197
111	651775F	27	1	GG	CC	CA	2	PVT.JOB	0	1	1	1	2	1	0	0	0	0	2	0	221
112	657780F	18	0	GG	CT	CA	1	STUDENT	0	1	1	1	2	1	0	0	0	0	1	0	11
113	657646F	33	1	GG	CT	CA	1	LABOURER	0	1	1	1	2	1	0	0	0	1	2	0	33
114	374690F	46	0	GG	CC	CC	8	HOUSE WIFE	3	1	1	1	1	1	1	0	0	0	3	1	221
115	657667F	80	1	GG	CC	AA	1	RETIRED	9	1	1	1	2	1	0	0	0	0	2	0	68
116	664561F	39	1	GG	CC	AA	1	BUSINESS	0	1	1	1	2	1	0	0	0	1	1	0	152
117	664773F	42	1	GG	CC	CC	1	BUSINESS	3	1	1	1	1	1	0	0	0	0	0	0	143
118	648456F	57	0	GG	CC	CC	2	HOUSE WIFE	1	1	1	1	4	1	0	0	0	0	3	1	221
119	664696F	81	1	GG	CC	AA	2	RETIRED	4	1	1	1	1	1	1	0	0	0	4	1	186
120	656335F	59	1	GG	CC	AA	5	RETIRED	3	2	1	1	50	0	0	0	1	0	2	0	26
121	671530F	26	1	GG	CC	CA	1	LABOURER	0	1	1	1	1	1	0	0	0	0	0	0	12
122	671549F	41	1	GG	CC	CC	2	MECHANIC	8	1	1	1	3	1	0	0	0	1	0	0	6
123	651467F	16	1	GG	CC	AA	6	STUDENT	0	2	1	1	60	1	0	0	0	0	0	0	16
124	671492F	33	1	GG	CC	CA	1	DRIVER	0	1	1	1	4	1	0	0	1	1	4	1	221
125	671445F	40	1	GG	CC	CC	1	BUSINESS	0	1	1	1	3	1	0	0	0	1	1	0	133
126	686767F	14	0	GG	CC	AA	2	STUDENT	0	1	1	1	4	1	0	0	0	0	0	0	3.4
127	671710F	54	0	GG	CT	CA	9	HOUSE WIFE	0	2	1	1	40	0	0	0	1	0	4	1	204
128	675380F	32	1	GG	CT	CA	1	LABOURER	0	1	1	1	4	1	0	0	1	1	2	0	86
129	682369F	27	1	GG	CC	CA	5	PVT.JOB	0	1	1	1	3	1	0	0	0	1	0	0	3.4
130	490309F	21	0	GG	CT	CC	2	HOUSE WIFE	0	1	1	1	4	1	0	0	0	0	1	0	68
131	682656F	35	1	GG	CC	CC	6	BUSINESS	0	2	1	1	100	1	0	0	0	1	0	0	79
132	683304F	54	1	GG	CT	CC	5	BUSINESS	0	2	0	1	40	1	1	0	0	1	3	1	111
133	675744F	12	0	GG	CT	CA	2	STUDENT	0	1	1	1	4	1	1	0	0	0	4	1	221
134	089408F	17	0	GG	CC	CC	2	STUDENT	0	1	1	1	2	1	0	0	1	0	0	0	3.4
135	688425F	45	0	GG	CC	AA	6	HOUSE WIFE	0	1	1	1	5	1	0	0	0	0	0	0	11.8
136	092121F	60	1	GG	CC	CA	5	BUSINESS	0	1	1	1	1	1	0	0	0	0	1	0	152
137	665492F	25	1	GG	CC	CC	6	BUSINESS	0	1	1	1	6	1	0	0	0	1	1	0	165
138	691534F	38	1	GG	CC	CA	6	PVT.JOB	0	1	1	1	1	0	0	0	0	0	1	0	34
139	139558D	26	1	GG	CC	CA	2	PVT.JOB	0	1	1	1	5	1	0	0	0	0	1	0	128
140	696359F	18	1	GA	CC	CA	5	STUDENT	0	1	1	1	10	1	0	0	0	0	0	0	3.2
141	696742F	34	1	GG	CT	CC	1	BUSINESS	0	1	1	1	6	1	1	0	0	1	3	1	221

142	650166F	39	1	GG	CC	AA	5	GOVT EMPLOYEE	11	1	1	1	3	1	0	0	0	0	1	0	28.9
143	696344F	32	1	GG	CC	CC	1	BUSINESS	0	1	1	1	3	1	0	0	0	1	1	0	30.5
144	632730F	50	1	GG	CC	CA	5	BUSINESS	0	1	1	1	1	1	0	0	0	0	2	0	21.4
145	696968F	58	1	GG	CC	AA	2	RETIRED	1	1	1	1	2	1	0	0	0	0	2	0	101
146	704207F	30	1	GG	CT	CA	1	BUSINESS	0	2	1	1	15	0	0	0	0	1	1	0	84.5
147	792196C	63	1	GG	CC	CA	5	RETIRED	9	1	1	1	2	1	1	0	0	0	3	1	3.4
148	718519C	68	1	GG	CC	CA	2	RETIRED	1	1	1	1	2	1	0	0	0	0	3	1	35.6
149	666608B	60	0	GG	CC	CA	2	HOUSE WIFE	0	1	1	1	3	1	0	0	0	0	3	1	16
150	713275F	54	1	GG	CT	CC	2	GOVT EMPLOYEE	4	1	1	1	3	1	1	0	0	1	5	1	173.4
151	434120F	63	1	GG	CC	CC	2	RETIRED	0	1	1	1	1	1	0	0	0	0	1	0	3.4
152	713124F	35	1	GG	CC	CC	2	PVT.JOB	0	1	1	1	2	1	0	0	0	1	0	0	134
153	045008C	38	0	GG	CC	CA	2	HOUSE WIFE	1	1	1	1	2	1	1	0	0	1	4	1	221
154	094919F	29	1	GG	CC	CC	1	PVT.JOB	0	1	1	1	2	1	0	0	0	0	2	0	190
155	426257F	41	1	GG	CC	CA	2	MECHANIC	3	1	1	1	10	1	0	0	0	1	4	1	197
156	071001F	43	0	GG	CT	CC	2	HOUSE WIFE	0	1	1	1	3	1	0	0	0	0	2	0	200
157	720583F	32	1	GG	CC	CC	2	GOVT EMPLOYEE	0	1	1	1	2	1	0	0	0	1	4	1	126
158	726540F	24	1	GG	CT	CC	2	FACTORY WORKER	0	2	1	1	30	1	0	0	0	1	1	0	75
159	720903F	62	1	GG	CC	CA	2	RETIRED	9	1	1	1	4	1	1	0	0	0	4	1	218
160	720819F	39	0	GG	CC	CA	5	HOUSE WIFE	0	1	1	1	3	1	0	0	0	0	0	0	161
161	720845F	35	1	GG	CC	CA	1	BUSINESS	0	1	1	1	4	1	1	0	0	1	2	0	221
162	720805F	54	1	GG	CC	CC	2	LABOURER	1	2	1	1	50	1	0	0	1	1	4	1	221
163	455329F	40	1	GG	CT	CC	2	LABOURER	4	1	1	1	4	1	0	0	0	1	3	1	116
164	726261F	33	1	GA	CT	CC	1	BUSINESS	0	1	1	1	7	1	1	0	0	0	4	1	194
165	323801F	24	1	GA	CC	CA	1	BUSINESS	0	1	1	1	4	1	0	0	0	1	0	0	5.8
166	726860F	57	1	GG	CC	CC	1	AGRICULTURE	9	1	1	1	3	1	1	0	0	0	4	1	78
167	726349F	43	1	GG	CT	CC	1	BUSINESS	3	1	1	1	7	1	1	0	1	1	3	1	221
168	740002F	24	1	GG	CC	CA	5	MECHANIC	0	1	1	1	4	1	0	0	0	1	0	0	4.6

AMYLASE	LIPASE	PCV	CXR	USG	CT	EFFUSSION	ARDS	GALL STONES	IHBRD	PANCREATIC EDEMA	ACUTE FLUID COLLECTION	NECROSIS	NECROTIC COLLECTION	PSEUDOCYST	WOPN	INFECTED NECROSIS	CHOLANGITIS	BACTEREMIA
601	1537	47	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1216	1616	30	1	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0
497	820	31	1	1	0	2	0	0	0	1	0	0	0	0	0	0	0	0
780	434	36	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
294	455	32	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0
1040	2034	63	1	1	1	1	0	0	0	1	1	1	0	0	0	0	0	0
155	404	39	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	53	37	1	1	0	0	0	1	0	1	0	0	0	1	0	0	0	0
1450	1950	36	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
1074	3740	37	1	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0
1010	1551	37	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
841	1206	36	1	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0
1827	6000	34	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
410	923	38	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0
220	316	33	1	1	1	2	0	0	0	0	0	0	0	1	0	0	0	0
262	433	41	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1957	2697	44	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
473	2195	54	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
224	165	37	1	1	1	2	0	0	0	1	1	1	0	0	0	0	0	0
281	282	51	1	1	0	2	0	1	0	1	0	0	0	0	0	0	0	0
2577	4588	50	1	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0
477	755	55	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
660	960	34	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
2803	1350	46	1	1	1	0	0	1	1	0	0	0	0	0	0	0	1	0
3026	6910	33	1	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0
67	73	43	1	1	1	2	1	0	0	1	1	1	0	0	0	1	0	0
1089	2232	38	1	1	0	2	0	1	0	1	1	0	0	0	0	0	0	0
559	1565	43	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
1892	2292	40	1	1	1	1	0	0	0	1	1	1	0	0	0	0	0	0
711	1207	56	1	1	1	2	0	0	0	1	1	1	0	0	0	0	0	0
497	1270	42	1	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0
205	133	54	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
432	1708	54	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
109	372	42	1	1	1	1	0	0	0	1	1	0	0	0	0	0	0	0
52	230	39	1	1	0	1	0	0	0	1	1	0	0	0	0	0	0	0
641	518	28	1	1	1	1	0	0	0	1	1	0	0	0	0	0	0	0
2824	3565	52	1	1	0	2	1	0	0	1	0	0	0	0	0	0	0	0
3148	9958	47	1	1	1	2	0	0	0	1	0	0	0	0	0	0	0	0
371	800	49	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
3772	7080	50	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0
866	2050	60	1	1	1	0	0	0	0	1	0	1	0	0	0	0	0	0
3440	1266	40	1	1	1	2	0	1	1	1	0	0	0	0	0	0	1	0
57	49	34	1	1	1	2	0	0	0	1	0	1	0	0	0	0	0	0
1579	1322	36.3	1	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0
531	2595	38	1	1	0	0	0	1	1	1	0	0	0	0	0	0	0	0
271	1064	42	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
766	599	55	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
1801	3600	32	1	1	1	1	0	0	0	1	1	1	1	0	0	0	0	0
2304	4160	46	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
2058	4091	40	1	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0
1500	2000	40.2	1	1	0	2	0	0	0	1	0	0	0	0	0	0	0	0
1133	1763	42.5	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0
77	145	51	1	1	0	2	0	0	0	1	0	0	0	0	0	0	0	0
428	600	42	1	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0
2314	3456	33	1	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0
1908	8930	40	1	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0
225	68	33	1	1	1	0	0	0	0	1	0	0	0	1	0	0	0	0
1596	759	31	1	1	1	0	0	0	0	1	0	1	0	1	0	0	0	0
171	1027	46	1	1	1	0	0	1	0	1	1	0	0	0	0	0	0	0
748	1000	50	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
350	1950	55	1	1	1	2	0	0	0	1	1	0	0	0	0	0	0	0
185	385	43	1	1	0	0	0	1	0	0	0	0	0	0	0	0	1	1
2197	7402	34	1	1	1	0	0	1	0	1	0	0	0	0	0	0	0	0
527	1008	49	1	1	1	2	0	0	0	1	1	1	0	0	0	0	0	0
709	3314	39	1	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0
1480	1200	40	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0
403	668	45	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
271	400	47	1	1	1	1	0	0	0	1	1	1	0	0	0	0	0	1
298	477	27	1	1	1	1	0	0	0	1	1	1	0	0	0	0	0	0
1094	949	33	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0

2053	4304	45	1	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0
867	955	44	1	1	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0
902	1463	53	1	1	1	2	0	0	0	1	1	1	0	1	1	0	0	0	0
1659	4381	38	1	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0
1924	4209	35	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
86	56	35	1	1	1	2	0	0	0	1	1	0	0	0	0	0	0	0	0
1715	3600	41	1	1	1	2	0	0	0	1	1	1	0	0	0	0	0	0	0
1730	4758	36	1	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0
534	920	42	1	1	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0
921	1790	58	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
2987	2392	34	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1
1789	2729	50	1	1	1	0	1	0	0	1	1	1	0	0	0	1	0	0	1
258	362	51	1	1	1	1	0	0	0	1	1	1	0	0	0	0	0	0	0
817	319	39	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
1810	4616	48	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
285	705	41	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
71	83	41	1	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
534	1217	54	1	1	1	2	0	0	0	1	1	1	0	1	0	0	0	0	0
1793	313	49	1	1	1	2	0	0	0	1	1	0	0	0	0	0	0	0	0
279	359	47	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
948	184	31	1	1	0	0	0	1	0	1	0	0	0	0	0	0	0	1	0
432	278	41	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
1782	2347	44	1	1	1	0	0	1	1	1	1	1	0	0	0	0	0	0	0
288	589	38	1	1	1	0	0	0	0	1	1	1	1	1	0	0	0	0	0
164	181	53	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
624	3525	35	1	1	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0
750	2236	31	1	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
381	834	45	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
454	591	36	1	1	1	2	0	0	0	1	0	1	0	1	1	1	0	0	0
1364	4636	45	1	1	1	0	0	0	1	1	0	0	0	0	0	0	1	0	0
213	167	37	1	1	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0
383	989	52	1	1	1	2	0	0	0	1	0	0	0	0	0	0	0	0	0
280	1024	48	1	1	1	0	0	1	1	1	0	0	0	0	0	0	1	1	1
234	400	45	1	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0
300	870	44	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
325	1396	38	1	1	0	0	0	1	1	1	0	0	0	0	0	0	1	0	0
64	78	19	1	1	1	0	1	1	1	1	0	1	0	0	0	1	0	1	1
568	1034	51	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
230	487	37	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
1029	1680	36	1	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0
566	1026	41	1	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
1776	2707	35	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
467	1145	32	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
750	1822	26	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1
332	232	37	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
292	749	51	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
1273	1455	48	1	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0
119	216	38	1	1	1	2	0	0	0	1	1	1	0	0	0	0	0	0	0
2271	4460	36	1	1	1	2	0	0	0	1	1	0	0	0	0	0	0	0	0
106	83	38	1	1	1	0	0	0	1	1	0	0	0	1	0	0	1	1	1
633	1493	48	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
429	1231	52	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
198	69	38	1	1	1	1	0	0	0	1	1	1	0	1	0	0	0	0	0
230	161	37	1	1	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0
283	810	36	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
108	193	36	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
96	27	21	1	1	1	2	0	1	0	1	0	1	0	0	0	1	0	0	0
315	111	38	1	1	0	2	0	0	0	1	1	0	0	0	0	0	0	0	0
227	32	47	1	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0
2540	6480	44	1	1	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0
129	651	39	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0
78	38	23	1	1	1	2	0	0	0	1	0	1	0	0	1	1	0	1	1
820	2198	41	1	1	0	2	0	1	0	1	1	0	0	0	0	0	0	0	0
3585	7684	33	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
124	176	34	1	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0
1450	1950	41	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
35	56	28	1	1	1	0	0	0	0	1	0	1	0	1	0	0	0	0	0
1286	1643	31	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
1885	3183	41	1	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0
1999	4448	39	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
128	359	46	1	1	1	2	0	1	0	1	1	1	0	0	0	0	0	0	0

549	339	42	1	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0
1138	2380	45	1	1	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0
771	2951	39	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
1590	1754	46	1	1	0	0	0	1	1	1	0	0	0	0	0	0	1	0	0
90	90	42	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0
1038	5540	30	1	1	0	1	0	1	0	1	1	0	0	0	0	0	0	0	0
3981	20890	49	1	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0
1113	6290	44	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
1047	3680	55	1	1	1	1	0	0	0	1	1	1	0	0	0	0	0	0	0
741	1320	43	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
444	588	43	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
147	1003	43	1	1	1	3	0	0	0	1	1	1	0	0	0	0	0	0	0
711	1373	51	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
62	105	40	1	1	1	1	0	0	0	1	1	0	0	0	0	0	0	0	1
1900	4560	39	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
520	878	62	1	1	1	2	0	0	0	1	0	1	0	0	0	0	0	0	0
681	289	39	1	0	1	1	0	0	0	1	0	1	0	0	1	0	0	0	0
5786	8146	48	1	1	0	2	0	1	0	1	1	0	0	0	0	0	0	0	0
1831	2070	38	1	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0
168	415	51	1	1	0	2	0	0	0	1	0	0	0	0	0	0	0	0	0
49	42	40	1	1	1	0	0	1	0	1	1	0	0	0	0	0	0	0	0
268	1100	36	1	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0
1324	1543	43	1	1	1	2	0	1	0	1	1	1	0	0	0	0	0	0	0
925	892	45	1	1	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0
1343	691	51	1	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
14	14	36	1	1	1	2	0	0	0	1	0	1	0	0	0	0	0	0	1
266	257	42	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0

ORGANISM	INFECTED COLLECTION	ORGANISM	ANTIBIOTIC USE	PANCREATIC ASCITIS	SV/PV /SMVTHROMBOSIS	HYPOTENSION	CREAT >1.9	ALI/ARDS	HOSPITAL STAY	ICU	ICU-DURATION	INOTROPES	VENTILATION
	0		0	0	0	0	0	0	1	0		0	0
	0		1	0	1	1	1	1	8	1	8	1	1
	0		0	0	0	0	0	1	1	0		0	0
	0		0	0	0	0	0	0	5	0		0	0
	0		0	0	0	0	0	0	6	0		0	0
	0		1	0	0	0	0	0	20	0		0	0
	0		0	0	0	0	0	0	1	0		0	0
	0		0	0	0	0	0	0	16	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		0	0	0	0	0	0	8	0		0	0
	0		0	0	0	0	0	0	6	0		0	0
	0		1	0	0	1	0	1	4	0		1	1
	0		1	0	0	0	0	0	8	0		0	0
	0		0	0	0	0	0	0	6	0		0	0
	0		1	1	0	1	0	0	42	0		1	0
	0		0	0	0	0	0	0	2	0		0	0
	0		0	0	0	0	0	0	8	0		0	0
	0		0	0	0	1	1	1	1	1	1	1	1
	0		1	0	1	0	0	1	11	0		0	0
	0		0	0	0	0	0	1	12	0		0	0
	0		0	0	0	0	0	0	10	0		0	0
	0		0	0	0	0	0	0	5	0		0	0
	0		0	0	0	0	0	0	8	0		0	0
	0		1	0	0	0	0	0	5	0		0	0
	0		1	0	0	0	0	0	9	0		0	0
	1	ENTEROCOCCUS,ECOLI, PSEUDOMONAS	1	0	0	1	0	1	37	1	36	1	1
	1	ENTEROBACTER	1	1	0	1	1	1	7	1	7	1	1
	0		0	0	0	0	0	0	4	0		0	0
	0		1	0	0	0	0	0	16	0		0	0
	0		1	0	3	0	0	1	13	0		0	0
	0		0	0	0	0	1	1		0		0	0
	0		0	0	0	1	0	1	6	1	5	1	1
	0		0	0	0	0	0	0	9	0		0	0
	0		0	0	0	0	0	1	7	0		0	0
	0		0	0	0	0	0	1	4	0		0	0
	0		0	0	0	0	0	1	7	0		0	0
	0		0	0	0	0	0	1	4	0		0	0
	0		1	0	0	0	0	0	14	0		0	0
	0		0	0	0	1	1	1	1	1	1	1	1
	0		0	0	1	0	0	1	11	0		0	0
	0		0	0	0	0	0	0	5	0		0	0
	0		0	0	0	0	0	0	5	0		0	0
	0		0	0	0	0	0	1	7	0		0	0
	0		1	0	0	0	0	0	11	0		0	0
	0		1	0	1	0	0	1	7	0		0	0
	0		0	0	0	0	0	0	5	0		0	0
	0		0	0	0	0	0	0	8	0		0	0
	0		0	0	0	0	0	0	3	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		0	0	1	0	0	1	17	1	5	0	1
	0		0	0	0	0	0	0	9	0		0	0
	0		0	0	0	0	0	0	9	0		0	0
	0		0	0	0	0	0	1	5	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		1	0	0	0	0	1	21	0		0	0
	0		0	0	0	0	0	0	6	0		0	0
	0		0	0	0	0	0	0	8	0		0	0
	0		0	0	0	0	0	0	5	0		0	0
	0		1	0	0	0	0	0	14	0		0	0
	0		0	0	1	0	0	0	18	0		0	0
	0		1	0	0	0	0	0	11	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		1	1	0	0	0	1	20	1	14	0	1
KLEBSIELLA	0		1	0	0	0	0	0	7	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		1	0	0	0	0	1	15	0		0	0
	0		0	0	0	0	0	0	6	0		0	0
	0		0	0	0	0	0	1	12	0		0	0
	0		0	0	0	0	0	0	3	0		0	0
ENTEROCOCCUS	0		1	1	2	1	1	1	8	1	8	1	1
	0		1	0	1	0	0	0	11	0		0	0
	0		0	0	0	0	0	0	7	0		0	0

	0		0	0	0	0	0	0	4	0		0	0
	0		1	0	0	0	1	1	8	1	7	0	1
	0		1	0	2	0	0	1	33	0		0	0
	0		0	0	0	0	0	0	9	0		0	0
	0		0	0	0	0	0	1	8	0		0	0
	0		1	0	0	0	0	0	7	0		0	0
	0		1	0	0	0	0	0	13	0		0	0
	0		0	0	0	0	0	0	2	0		0	0
	0		1	0	0	0	0	1	11	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
E.COLI	0		1	0	0	0	1	1	8	0		0	0
SALMONELLA	1	KLEBSIELLA,ENTEROBACTER	1	0	0	0	1	1	33	1	27	0	1
	0		1	0	0	0	0	0	10	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		0	0	0	0	0	0	2	0		0	0
	0		0	0	0	0	0	0	3	0		0	0
	0		0	0	0	0	0	0	12	0		0	0
	0		0	0	1	0	0	0	11	0		0	0
	0		1	1	3	0	0	1	32	1	8	0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		1	0	0	0	0	1	21	0		0	0
	0		0	0	0	0	0	0	3	0		0	0
	0		0	0	0	0	0	1	13	0		0	0
	0		0	1	0	0	0	1	7	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		1	0	0	1	0	0	8	0		1	0
	0		1	0	0	1	1	1	7	1	1	1	1
	0		0	0	0	0	0	0	5	0		0	0
	0		1	0	1	0	1	0	14	0		0	0
	0		1	0	0	0	0	0	11	0		0	0
	0		0	0	0	0	0	1	8	0		0	0
	0		0	0	0	0	0	1	7	0		0	0
	0		1	0	0	0	0	0	10	0		0	0
	0		1	0	0	1	1	1	23	1	23	1	1
	0		0	0	0	0	0	1	3	0		0	0
	0		1	0	0	0	0	0	5	0		0	0
	0		0	0	0	0	0	1	3	0		0	0
	0		1	0	0	0	0	0	5	0		0	0
ENTEROBACTER	1	KLEBSIELLA, E.COLI	1	0	4	1	0	1	58	1	46	1	1
	0		0	0	0	0	0	1	8	0		0	0
	0		0	0	0	0	0	0	5	0		0	0
	0		1	0	0	0	0	1	14	0		0	0
	0		0	0	0	0	0	1	8	0		0	0
	0		0	0	0	0	0	0	5	0		0	0
	0		0	0	0	0	0	1	7	1	3	0	0
E.COLI	0		1	0	0	0	0	1	16	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		0	0	0	0	0	0	6	0		0	0
	0		1	0	0	0	0	1	16	0		0	0
	0		0	0	1	0	0	1	8	0		0	0
E.COLI	0		1	0	0	0	0	0	16	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		0	0	0	0	0	0	3	0		0	0
	0		0	0	0	0	0	1	30	0		0	0
	0		1	0	0	0	0	1	17	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	1	E.COLI	1	0	0	0	0	1	44	0		0	0
	0		0	0	0	0	0	0	9	0		0	0
	0		0	0	1	0	0	0	4	0		0	0
	0		0	0	0	0	0	0	9	0		0	0
	0		1	0	0	0	0	0	30	0		0	0
	0		1	0	1	0	0	0	40	1	20	0	0
	0		0	0	0	0	0	1	8	0		0	0
	0		1	0	0	0	0	0	7	0		0	0
	0		0	0	0	0	0	0	13	0		0	0
	0		0	0	0	0	0	0	7	0		0	0
	0		0	0	1	0	0	0	8	0		0	0
	0		0	0	0	0	0	0	8	0		0	0
	0		0	0	0	0	0	0	6	0		0	0
	0		0	0	0	0	0	0	10	0		0	0
	1	E.COLI	1	0	1	0	0	1	30	0		0	0

	0		1	0	0	0	0	0	8	0		0	0
	0		0	0	0	0	0	0	8	0		0	0
	0		0	0	0	0	0	0	7	0		0	0
	0		1	0	0	0	0	0	7	0		0	0
	0		0	0	1	0	0	0	12	0		0	0
	0		0	0	0	0	0	1	12	0		0	0
	0		0	0	0	0	0	0	6	0		0	0
	0		0	0	0	0	0	0	7	0		0	0
	0		1	0	1	0	0	1	18	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		0	0	0	0	0	1	8	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
STAPH.AUREUS	0		1	0	0	0	0	1	16	0		0	0
	0		0	0	0	0	0	0	7	0		0	0
	0		0	0	1	0	0	1	7	0		0	0
	0		0	0	0	0	0	0	6	0		0	0
	0		0	0	0	0	0	1	14	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		0	0	0	0	0	1	8	0		0	0
	0		1	0	0	0	0	1	20	0		0	0
	0		0	0	0	0	0	0	3	0		0	0
	0		1	0	1	0	0	1	11	0		0	0
	0		0	0	0	0	0	0	4	0		0	0
	0		0	0	0	0	0	0	5	0		0	0
BURKHOLDERIA	0		1	0	1	0	0	1	12	0		0	0
	0		0	0	0	0	0	0	5	0		0	0

DIALYSIS	LOCAL COMPLICATION	SYSTEMIC COMPLICATION	TRANSIENT/PERSISTANT	GI BLEED	FEEDING	SURGERY	DEATH/DAMA	ETIOLOGY	RECURRENT	SEVERITY
0	0	0		0	2	0	0	ALCHOHOL	1	1
1	0	1	2	0	3	0	1	GALLSTONE, HYPERCALCEMIA	0	3
0	0	1	2	0	1	0	0	ALCHOHOL	0	3
0	0	0		0	2	0	0	IDIOPATHIC	1	1
0	0	0		0	3	0	0	ALCHOHOL	0	1
0	1	0		0	3	0	0	ALCHOHOL	0	2
0	0	0		0	2	0	0	ALCHOHOL	0	1
0	1	0		0	2	0	0	GALLSTONE	0	2
0	0	0		0	2	0	0	IDIOPATHIC	1	1
0	1	0		0	2	0	0	IDIOPATHIC	0	2
0	0	0		0	2	0	0	ART INDUCECD	0	1
0	1	1	2	0	1	0	1	IDIOPATHIC	0	3
0	0	0		0	2	0	0	POST ERCP	0	1
0	0	0		0	2	0	0	IDIOPATHIC	1	1
0	1	1	2	0	3	0	0	ALCHOHOL	0	3
0	0	0		0	2	0	0	IDIOPATHIC	1	1
0	0	0		0	2	0	0	ANATOMIC ABNORMALITY	1	1
0	0	1	2	0	1	0	1	ALCHOHOL	0	3
0	1	1	2	0	3	0	0	ALCHOHOL	0	3
0	0	1	1	0	3	0	0	HYPERPARATHYROIDISM	0	2
0	0	0		0	2	0	0	GALLSTONE	0	1
0	0	0		0	2	0	0	ALCHOHOL	0	1
0	0	0		0	3	0	0	HYPERPARATHYROIDISM	1	1
0	0	0		0	2	0	0	GALLSTONE	0	1
0	0	0		0	2	0	0	GALLSTONE	0	1
0	1	1	2	1	3	1	2	ALCHOHOL	0	3
0	1	1	2	0	1	0	1	GALLSTONE	0	3
0	0	0		0	2	0	0	ALCHOHOL	0	1
0	1	0		0	3	0	0	ALCHOHOL	0	2
0	1	1	2	1	3	0	0	ALCHOHOL	0	3
0	0	1	2	0	1	0	0	ART INDUCECD	0	3
0	0	1	2	0	1	0	1	IDIOPATHIC	0	3
0	0	0		0	3	0	0	ALCHOHOL	1	1
0	1	1	1	0	2	0	0	ALCHOHOL	0	2
0	1	1	1	0	2	0	0	ALCHOHOL	0	2
0	1	0		0	2	0	0	CHEMOTHERAPY	0	2
0	1	1	1	0	2	0	0	ALCHOHOL	0	2
0	1	0		0	2	0	0	CHEMOTHERAPY	0	2
0	0	1	2	0	1	0	1	ALCHOHOL	0	3
0	1	1	1	0	2	0	0	IDIOPATHIC	0	2
0	0	0		0	2	0	0	ALCHOHOL	1	1
0	0	0		0	2	0	0	ALCHOHOL	1	1
0	1	1	1	0	1	0	0	ALCHOHOL	1	2
0	0	0		0	2	0	0	GALLSTONE	0	1
0	1	1	1	0	2	0	0	ALCHOHOL	1	2
0	0	0		0	2	0	0	HYPERPARATHYROIDISM	0	1
0	0	0		0	2	0	0	GALLSTONE	0	1
0	0	0		0	2	0	0	ALCHOHOL	0	1
0	0	0		0	2	0	0	ALCHOHOL	1	1
0	1	1	2	0	3	0	0	IDIOPATHIC	0	3
0	0	0		0	3	0	0	ALCHOHOL	0	1
0	0	0		0	2	0	0	GALLSTONE	0	1
0	0	1	1	0	2	0	0	IDIOPATHIC	1	2
0	0	0		0	2	0	0	IDIOPATHIC	0	1
0	0	1	2	0	2	0	0	ALCHOHOL	0	3
0	0	0		0	2	0	0	GALLSTONE	0	1
0	0	0		0	2	0	0	GALLSTONE	0	1
0	0	0		0	2	0	0	GALLSTONE	0	1
0	1	0		0	2	2	0	ALCHOHOL	0	2
0	1	0		0	3	0	0	ALCHOHOL	0	2
0	1	0		0	3	0	0	GALLSTONE	0	2
0	0	0		0	2	0	0	ALCHOHOL	0	1
0	1	1	2	0	3	0	0	ALCHOHOL	0	3
0	0	0		0	2	0	0	GALLSTONE	0	1
0	0	0		0	2	0	0	GALLSTONE	1	1
0	1	1	2	0	3	0	2	ALCHOHOL	0	3
0	0	0		0	2	0	0	GALLSTONE	0	1
0	0	1	2	0	3	0	0	ALCHOHOL	0	3
0	0	0		0	2	0	0	ALCHOHOL	0	1
0	1	1	2	0	3	0	1	ALCHOHOL	0	3
0	1	0		0	3	0	0	ALCHOHOL	0	2
0	0	0		0	3	0	0	ALCHOHOL	0	1

0	1	0		0	2	0	0	ALCHOHOL	0	2
1	1	1	2	0	3	0	2	ALCHOHOL	0	3
0	1	1	2	0	3	0	0	ALCHOHOL	1	3
0	1	0		0	3	0	0	IDIOPATHIC	0	2
0	0	1	1	0	2	0	0	IDIOPATHIC	0	2
0	1	0		0	3	0	0	ALCHOHOL	1	2
0	1	0		0	3	0	0	IDIOPATHIC	1	2
0	0	0		0	2	0	0	GALLSTONE	0	1
0	1	1	2	0	3	0	0	ALCHOHOL	1	3
0	0	0		0	2	0	0	ALCHOHOL	0	1
0	0	1	2	0	2	0	0	IDIOPATHIC	0	3
1	1	1	2	0	3	0	1	ALCHOHOL	0	3
0	1	0		0	2	0	0	ALCHOHOL	0	2
0	0	0		0	2	0	0	IDIOPATHIC	0	1
0	0	0		0	2	0	0	IDIOPATHIC	1	1
0	0	0		0	2	0	0	IDIOPATHIC	0	1
0	1	0		0	3	0	0	ALCHOHOL	0	2
0	1	0		0	3	1	0	ALCHOHOL	1	2
0	1	1	2	0	3	0	0	ALCHOHOL	0	3
0	0	0		0	2	0	0	ALCHOHOL	0	1
0	0	1	2	0	3	0	0	GALLSTONE	0	2
0	0	0		0	2	0	0	GALLSTONE	0	1
0	1	1	2	0	2	0	0	GALLSTONE	0	3
0	1	1	1	0	3	0	0	GALLSTONE	0	2
0	0	0		0	3	0	0	ALCHOHOL	0	1
0	0	1	2	0	0	0	0	IDIOPATHIC	0	3
0	0	1	2	0	3	0	1	LAMIVUDINE	0	3
0	0	0		0	2	0	0	ALCHOHOL	0	1
0	1	1	2	0	3	0	2	ALCHOHOL	0	3
0	0	0		0	2	0	0	IDIOPATHIC	1	1
0	1	1	1	0	2	0	0	IDIOPATHIC	0	2
0	0	1	1	0	2	0	0	ALCHOHOL	0	2
0	0	1		0	2	0	0	GALLSTONE	0	1
0	0	1	2	0	3	0	1	ALCHOHOL	0	3
0	0	1	1	0	2	0	0	ALCHOHOL	0	2
0	0	0		0	2	0	0	GALLSTONE	0	1
0	1	1	2	1	3	1	0	GALLSTONE	0	3
0	0	1	1	0	3	0	0	ALCHOHOL	0	2
0	0	0		0	2	0	0	IDIOPATHIC	0	1
0	1	1	2	0	2	0	0	IDIOPATHIC	0	3
0	0	1	1	0	2	0	0	IDIOPATHIC	0	1
0	0	0		0	2	0	0	IDIOPATHIC	0	1
0	0	1	2	0	2	0	0	ALCHOHOL	0	3
0	0	1	2	0	3	0	0	POST ERCP	0	3
0	0	0		0	2	0	0	IDIOPATHIC	0	1
0	0	0		0	2	0	0	ALCHOHOL	0	1
0	0	0		0	2	0	0	AMPULLARY GROWTH	0	1
0	1	1	2	0	3	0	0	IDIOPATHIC	0	3
0	1	1	1	0	3	0	0	IDIOPATHIC	0	2
0	1	0		0	0	0	0	IDIOPATHIC	0	2
0	0	0		0	3	0	0	IDIOPATHIC	0	1
0	0	0		0	2	0	0	ALCHOHOL	0	1
0	1	1	2	0	3	0	0	IDIOPATHIC	0	3
0	1	1	1	0	3	0	0	ALCHOHOL	0	2
0	0	0		0	2	0	0	ALCHOHOL	0	1
0	0	0		0	2	0	0	IDIOPATHIC	0	1
0	1	1	2	0	3	0	0	GALLSTONES	0	3
0	1	0		0	3	0	0	ALCHOHOL	1	2
0	1	0		0	3	0	0	ALCHOHOL	1	2
0	1	0		0	3	0	0	IDIOPATHIC	0	2
0	1	0		0	3	0	0	ALCHOHOL	0	2
0	1	1	2	0	3	0	2	ALCHOHOL	0	3
0	1	1	1	0	2	0	0	IDIOPATHIC	0	2
0	0	0		0	2	0	0	IDIOPATHIC	1	1
0	0	0		0	2	0	0	HYPERPARATHYROIDISM,GALLSTONES	0	1
0	0	0		0	2	0	0	IDIOPATHIC	0	1
0	1	0		0	3	0	0	ALCHOHOL	0	2
0	0	0		0	2	0	0	POST ERCP	0	1
0	1	0		0	2	0	0	IDIOPATHIC	1	2
0	0	0		0	2	0	0	HEPATITIS B	0	1
0	1	1	2	0	3	0	0	ALCHOHOL, GALL STONES	0	3

0	1	0		0	3	0	0	DRUG INDUCED	0	2
0	1	0		0	2	0	0	ALCHOHOL	0	2
0	0	0		0	2	0	0	POST ERCP	0	1
0	0	0		0	2	0	0	GALL STONE	0	1
0	1	0		0	2	0	0	ALCHOHOL	0	2
0	1	1	1	0	2	0	0	GALL STONE	0	2
0	0	0		0	3	0	0	GALL STONE	0	1
0	0	0		0	2	0	0	DRUG INDUCED	0	1
0	1	1	2	0	3	0	0	ALCHOHOL	0	3
0	0	0		0	2	0	0	IDIOPATHIC	0	1
0	0	0		0	2	0	0	ALCHOHOL	0	1
0	1	1	1	0	3	0	0	IDIOPATHIC	0	2
0	0	0		0	2	0	0	IDIOPATHIC	1	1
0	1	1	2	0	3	0	0	ALCOHOL	0	3
0	0	0		0	2	0	0	IDIOPATHIC	0	1
0	1	1	1	0	2	0	0	ALCOHOL	0	2
0	1	0		0	2	0	0	ALCOHOL	0	2
0	1	1	2	0	3	0	0	GALL STONE	0	3
0	0	0		0	2	0	0	GALL STONE	1	1
0	0	1	1	0	2	0	0	ALCOHOL	0	2
0	1	1	2	0	3	0	0	ALCOHOL,GALL STONE	0	3
0	1	0		0	2	0	0	ALCOHOL	0	2
0	1	1	2	0	3	0	0	GALL STONE	0	3
0	1	0		0	2	0	0	ALCOHOL	0	2
0	0	1	1	0	2	0	0	IDIOPATHIC	0	2
0	1	1	2	0	3	0	0	ALCOHOL	0	3
0	0	0		0	2	0	0	ALCOHOL	1	1

STATE-	1-AP	2-TAMIL NADU	3- BIHAR	4-KARNATAKA	5- WEST BENGAL	6-JHARKHAND	7-UP	8-TRIPURA	9-SIKKIM		
PRESENTATION	1=ACUTE EPISODE	2-COMPLICATION									
EFFUION	0-NIL	1-LEFT SIDED	2-BILATERAL								
SV/PVTHROMBOSIS	0-NIL	1-SPLENIC VEIN	2-PORTAL VEIN	3-SMV	4-JEJUNAL ARTERY ANEURYSM						
TRANSIENT/PERSISTANT	1-TRANSIENT	2-PERSISTANT									
SEVERITY	1- MILD	2-MODERATE	3-SEVERE								
DEATH/DAMA	0-ALIVE	1-DEATH	2-DAMA								
COMORBIDITIES	1-HTN	2-RETRO VIRAL DISEASE	3-DM	4-DM&HTN	5- IHD	6- AML	7-DM, HTN, ASTHMA	8- CHRONIC HEP B	9-ASTHMA/COPD	10- HYPOTHYROID	11-CA STOMACH
FEEDING	1-IV FLUIDS	2-ORAL	3- NJ	4-TPN							
SURGERY	0- NO	1-0PEN	2-ENDOSCOPIC DRAINAGE								
SGS SCORE	0-9										
PANCREATIC EDEMA	0- NO	1-YES									
ACUTE FLUID COLLECTION	0-N0	1-YES									
NECROSIS	0-NO	1-YES									
NECROTIC COLLECTION	0=NO	1-YES									
PSEUDOCYST	0-NO	1-YES									
WOPN	0-N0	1-YES									
INFECTED NECROSIS	0-N0	1-YES									
LOCAL COMPLICATION	0-NO	1-YES									
SYSTEMIC COMPLICATION	0-NO	1-YES									
ICU STAY	0- NO	1-YES									
RECURRENT	0- FIRST EPISODE	1- RECURRENT ATTACK									